New Jersey Division of Mental Health Services

Pharmacological Practice Guidelines for the Treatment of Schizophrenia

2005 Edition

DMHS Practice Guidelines Workgroup

Robert Eilers, M.D., MPH, Medical Director, Division of Mental Health Services, Chair

Maria Cutie, R.Ph., MS, CCP, Coordinator of Pharmacy Services, Department of Human Services

Linda Gochfeld, M.D., Medical Director, SERV Behavioral Health System, Inc.

Stephen Gootblatt, M.D., Chief of Medicine, Greystone Park Psychiatric Hospital

Marie Elena Hasson, M.D., Chief of Psychiatry, Ancora Psychiatric Hospital

Elizabeth Levin, M.D., Associate Clinical Professor, University of Medicine and Dentistry of New Jersey

Margaret Molnar, Special Assistant to the Director for Consumer Affairs, Division of Mental Health Services

Jeffry Nurenberg, M.D., Medical Director, Greystone Park Psychiatric Hospital

Sasi Pasupuleti, M.D., Chief of Psychiatry, Ann Klein Forensic Center

Karen Piren, R.N., A.P.N., C., Liaison, Division of Mental Health Services

Shahida Siddiqui, M.D., Chief of Psychiatry, Trenton Psychiatric Hospital

Harry A. Thibodeau, R.Ph., CCP, FASCP, Vice President of Government Affairs, Pharma-Care, Inc.

Rafael Tortosa, M.D., Medical Director, Hagedorn Psychiatric Hospital

Michael Walsh, M.P.A., Administrative Analyst I (Data Processing), Division of Mental Health Services

Disclaimer

These practices guidelines are not intended to serve as a standard fo medical care. Such standards are determined on the basis of the clinical data available for individual cases and are subject to change as scientific knowledge advances and as patterns of care evolve. These guidelines are based on the available evidence at the time of their development. Division of Mental Health Services in not liable for unintended or adverse consequences that may occur from their use by practitioners.

New Jersey
Division of Mental Health Services
PO Box 727
50 East State Street
Trenton, New Jersey 08627-0727

Copy Editor

Margaret Adamick, R.Ph., CCP, Pharma-Care, Inc.

Cover Design

Barry Heil, Pharma-Care, Inc.

Graphic Design

Information Systems & Technology Department, Pharma-Care, Inc.
136 Central Avenue
Clark, NJ 07066

Table of Contents

INTRODUCTION

A multidisciplinary workgroup, consisting of individuals from New Jersey State psychiatric hospitals, the Division of Mental Health Service's central office, and the provider community, reviewed medical literature to develop these DMHS Pharmacological Practice Guidelines for the Treatment of Schizophrenia (Guidelines). These Guidelines should help clinicians make the complex decisions needed to treat patients with schizophrenia and insure that their prescribing practices are consistent with the evidence-based literature.[1] In addition, by defining practice standards for the pharmacological treatment of schizophrenia, the Guidelines will structure orientation and training for clinicians;[2] provide objective treatment goals and allow outcome measurement; and guide quality improvement and monitoring of cost-effective prescribing.

The workgroup has incorporated the best features of other previously published guidelines, especially those originating from the American Psychiatric Association, New York and Texas.[3] In addition to offering a concise and user-friendly format, the Guidelines represent the strengths of the research evidence supporting each of the treatment recommendations. [4] Practitioners should turn to other sources for evidence-based psychosocial and behavioral interventions for treating schizophrenia.

Whenever possible, recommendations are based on randomized, controlled clinical trials. However, because of limited availability of such evidence, clinicians need to consider other less reliable sources as well. When these Guidelines make a specific treatment recommendation, the strength of the evidence supporting it is indicated in parentheses, followed by footnoted references. The Guidelines use a standard classification similar to that used in other evidence-based practice guidelines.[5]

Levels of Evidence

Grade A:	Good research-based evidence (at least one randomized, controlled clinical trial or a meta-analysis)
Grade B:	Fair research-based evidence (nonrandomized, controlled trial or quasi-experimental studies)
Grade C:	Minimal research-based evidence (non-experimental descriptive studies), or based entirely on expert consensus

DMHS clinicians are expected to adhere to these Guidelines when prescribing medications to adult patients with schizophrenia, schizoaffective, and schizophreniform disorders. These recommendations do not apply to patients with other psychotic disorders, such as bipolar disorder; so individuals treated with these Guidelines must first be carefully assessed and have their diagnoses confirmed. While these Guidelines allow practitioners to prescribe any antipsychotic (AP), the recommendation is that these decisions be made collaboratively with the patient, and be based on past treatment response and individual preferences, as well as the side effect profiles and costs of alternative treatments.

The Guidelines make the recommendation that atypical APs should be considered first, especially if a patient has had no adequate trial of an atypical AP, because these agents demonstrate better side effect profiles (Grade C evidence).[6] However, these Guidelines recognize that, except for the proven superiority of clozapine in individuals with an inadequate response to other APs (Grade A), inconclusive evidence exists on the superior efficacy of the other atypicals over conventional APs (Grade C). Therefore, the Guidelines do not require that atypical APs be used first.[7]

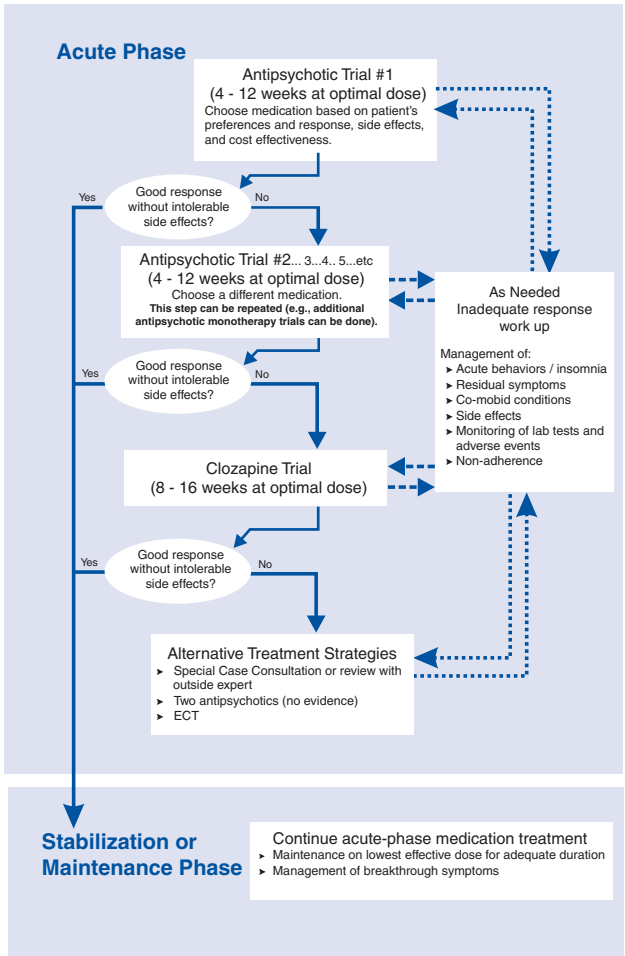
This evidence-based approach of the Guidelines supports AP monotherapy, with gradual titration to the lowest effective AP dose (Grade A).[8] While adding a conventional agent to a trial of an atypical AP has become a common practice in treating individuals with schizophrenia, no current research base exists for such

a practice. Furthermore, use of APs in combinations can lead to additive side effects, drug/drug interactions, difficulties when adjusting dosages, and adherence problems, in addition to increased costs.[9] Therefore, the Guidelines recommend that the combination of two APs should not be tried until after two trials of AP monotherapy and a trial on clozapine (Grade B).[10]

The Guidelines endorse the use of various strategies to manage residual positive/negative symptoms and mood lability, as well as, co-occurring disorders, such as major depression, obsessive-compulsive disorder, and substance abuse disorder. However, the evidence for these recommendations is minimal; thus, althought anticonvulsants have been used as adjunctive agents in schizophrenia, their use has not been shown to be as effective as that of clozapine, for example.. Finally, the Guidelines contain protocols to assess and manage a variety of side effects and treatment complications, including medication non-adherence associated with the APs. The protocols make recommendations for laboratory monitoring of patients on AP therapy. They also contain a new assessment tool for tardive dyskinesia; while less likely to occur with the atypical APs than with conventional APs, this disorder is still seen, despite the widespread use of atypical agents.[11]

The Guidelines promote the use of a problem checklist to obtain patient feedback on side effects. This requires that clinicians ask patients about their response to treatment. The DMHS will also be providing practitioners with materials to assist them with educating their patients about medications. By encouraging practitioners to collaborate with patients in treatment decisions, the Guidelines are consistent with a recovery model. Practitioners are asked to routinely complete symptom ratings on patients and to document these and other important clinical data in their structured monthly psychiatric progress notes.[12]

Medication Information Tables in the Guidelines provide comprehensive prescribing information about APs, antidepressants, mood stabilizers, and agents for the treatment of motor side effects. New atypical agents, aripiprazole, and depot risperidone have just been released with this publication, and clinicians are urged to be cautious about prescribing these agents until more information becomes available.[13] The Guidelines workgroup will periodically review and update the Guidelines to incorporate new findings. Comments and suggestions about the Guidelines should be sent to the Medical Director, DMHS at 50 East State Street, PO Box 727, Trenton, New Jersey, 08625-0727.


Acute Phase
Antipsychotic Trial #1
(4 - 12 weeks at optimal dose)
Choose medication based on patient's preferences and response, side effects, and cost effectiveness.
Yes
Good response without intolerable side effects?
No
Antipsychotic Trial #2... 3...4.. 5...etc
(4 - 12 weeks at optimal dose)
Choose a different medication.
This step can be repeated (e.g., additional antipsychotic monotherapy trials can be done).
As Needed
Inadequate response
work up
Management of:
Acute behaviors / insomnia
Residual symptoms
Co-mobid conditions
Side effects
Monitoring of lab tests and adverse events
Non-adherence
Yes
Good response without intolerable side effects?
No
Clozapine Trial
(8 - 16 weeks at optimal dose)
Yes
Good response without intolerable side effects?
No
Alternative Treatment Strategies
Special Case Consultation or review with outside expert
Two antipsychotics (no evidence)
ECT
Stabilization or
Maintenance Phase
Continue acute-phase medication treatment
Maintenance on lowest effective dose for adequate duration
Management of breakthrough symptoms

OVERVIEW

The Guidelines consist of a set of recommendations that are illustrated by an algorithm (flow chart on page 4) that distinguishes acute and maintenance phases of treatment. Throughout the acute and maintenance phases, practitioners should refer to protocols to help manage various complications of AP therapy. Decisions should be based on the objective and subjective assessments of treatment response.

- After confirming the diagnosis of schizophrenia, schizoaffective or schizophreniform disorder and prior to beginning therapy, practitioners should review the history of previous medication trials by talking to the patient, contacting the patient's treating physician(s), contacting family/significant others, and by obtaining medical records.

- For a patient with multiple previous trials of medication, select medication according to patient preferences, medication side-effect profiles, history of past response, and cost effectiveness. Give preference to use of an atypical AP if there is no reason to use a conventional agent, because atypical APs have more favorable side effect profiles.

- For a first break patient, start at the top of the treatment sequence and use an atypical agent at a dose at the lowest end of the recommended range (Grade B).[14] If history indicates that an adequate trial of an AP has been completed and the patient has failed to respond to that AP, this may allow earlier stages in the treatment sequence to be skipped.

- Start the patient on antipsychotic monotherapy for a period of at least four weeks and assess response. If needed at this or any later stages, conduct a work-up for inadequate response, or treat residual or co-occurring disorders, as needed.

- As much as possible, patients shall receive an adequate trial of an AP. AP trials should last at least 4-12 weeks (clozapine trials should last 8-16 weeks) (Grade B).[15]

- Go to the next stage of treatment, monotherapy with another antipsychotic, if a full response is not seen or if intolerable side effects

occur.[16] **If these do not occur and the response is good, go onto the maintenance phase.**

- After at least two trials of antipsychotic monotherapy, a clozapine trial should be attempted.[17] If the response is not good or intolerable side effects occur, or if a trial cannot be attempted because the patient refuses clozapine, go to the stage with alternative treatment strategies,[18] including ECT.[19]

- Follow the protocols for Monitoring and Laboratory Testing Protocols for APs (pages 36-38), including the AIMs+EPS.

- Have patients self report response to therapy and side effects using the Problem Reporting Checklist (page 59).

- Rate patient's symptoms at baseline (admission) and monthly using the Positive Symptom Rating Scale and Brief Negative Symptom Assessment (page 62).

EXAMPLES OF USING THE TREATMENT SEQUENCE

Example 1:

A 45-year old man with schizophrenia has been maintained on haloperidol decanoate 150 mg. monthly for the past three months but still has some paranoid thinking and bizarre behavior. He has a history of multiple hospitalizations, homelessness, intermittent substance use, and intermittent non-adherence to medications. He may have underlying cirrhosis as a result of long-term alcohol use. Previous trials of medication include haloperidol po, chlorpromazine, fluphenazine, and risperidone of unknown doses and duration.

Is the current AP an adequate trial? Yes, since the dose is adequate and duration of use exceeds six weeks.

Did the patient respond to the trial and tolerate the drug? If the patient is judged to have had a poor response to this trial, conduct an Inadequate Response Workup. If negative, go on to the next step and prescribe another AP. Aside from the current trial, we do not know enough about any of his previous trials to determine whether these were adequate, so an atypical agent should be considered. If, by history and further assessment, the patient is judged to have had a partial response, then you can consider maintaining the patient on haloperidol. However,

because of the patient's age and medical condition, monitor blood levels and consider lowering the dose.

Example 2:

A 21-year old woman with schizophrenia has been maintained for the past year on 6 mg. of risperidone. She presents with a dysphoric mood, suicidal ideation, and mild paranoid ideation. There is no history of substance abuse and she has not had any apparent side effects.

Is this an adequate trial? Yes, risperidone dose is neither too high nor too low, and duration exceeds six weeks.

Did the patient respond to the trial and tolerate the drug? Since the patient has tolerated the AP and has had at least a partial response to the trial, conduct an Inadequate Response Workup. Depending on the findings, treatment for the co-occurring depression may require a mood stabilizer or an SSRI. If the patient does not have a satisfactory response to this treatment, consider a trial with another AP.

Example 3:

A 38-year old man with schizophrenia presents with significant positive and negative symptoms and is low functioning. He has been treated with a combination of olanzapine 40 mg. and valproic acid 750 mg. for the past six months. He has a history of multiple long-term hospitalizations, and his record indicates he previously had multiple trials of conventional agents that were adequate in dose and duration.

Does the combined use of olanzapine and valproic acid constitute an adequate trial? The dose of the olanzapine is higher than recommended (20 mg. maximum), but the AP dose and duration requirements are met. The duration and dose of the valproic acid are adequate, but blood levels should be checked.

Is the response adequate and is the regimen being well tolerated? If the trial of Olanzapine has been adequate, but with no response, consider a trial of another AP, which would likely be clozapine, especially if the patient did not appear to respond to other AP trials of adequate dose and duration.

MANAGEMENT OF ACUTE PROBLEMS

AGITATION AND AGGRESSION[20]

Assessment / Non-pharmacological Management	Pharmacological Management
Determine the basis for the patient's agitation or aggression. Rule out as causes of agitation, medical problems and adverse effects from medications. Use verbal and environmental interventions before medications or physical interventions Use calming and supportive techniques. Offer the patient the opportunity to go to a quiet place or otherwise remove him/herself from the area. Only use physical interventions (seclusion and restraint) when the patient presents an immediate and serious danger to him/herself or others	Adjust current medication regimen (e.g. if an SSRI is causing restlessness, try giving all or some of the dose in the am; treat akathisia with beta blockers). Benzodiazepines alone or in combination with APs are the treatment of choice, with route of administration depending on the degree of agitation and available formulations of the drugs. Among the benzodiazepines, lorazepam (Ativan) is the recommended drug as it is relatively safe, fast-acting and effective in controlling psychotic agitation because it has a parenteral form that is well-absorbed. Lorazepam is the recommended drug for Stat use when treating agitation and aggressive behavior (Grade B) Dose Ranges: lorazepam 1-2mg PO or IM (0.5-1mg in elderly) can be given up to q2 hours. When a parenteral AP is indicated, use haloperidol IM 1-2 mg (can be given in same syringe as lorazepam). An alternative is ziprasidone (10–20 mg) IM. If a concentrate can be used, alternatives include risperidone concentrate, risperidone M tab and olanzapine sublingual tabs (Zyprexa Zydis). When a parenteral AP is indicated, use haloperidol IM 1-2 mg (can be given in same syringe as lorazepam). An alternative is ziprasidone (10–20 mg) IM or olanzapine (5-10 mg) IM.

Assessment / Non-pharmacological Management	Pharmacological Management
	If a concentrate can be used, alternatives include risperidone concentrate, risperidone M tab and olanzapine sublingual tabs (Zyprexa Zydis). If the response to lorazepam is inadequate and the acute behavioral problem persists, a Stat dose of the patients AP medication can be given alone or along with lorazepam. Avoid use of PRN antipsychotics when possible because psychotic symptoms require a period of time to remit. Intermittent dosing with PRN APs is unlikely to improve psychosis and may confuse the picture or cause untoward side effects. Benzodiazepines may need to be slowly tapered as agitation diminishes.If agitation or aggression becomes a persistent problem, consider treating as a co-occurring disorder/symptom.

INSOMNIA[21]

Assessment / Non-pharmacological Management	Pharmacological Management
Determine whether insomnia is due to situational stressors, daytime inactivity/naps, drinking caffeinated beverages in the evening, anxiety disorder, akathisia, hypomania, restlessness secondary to SSRI, nocturnal myoclonus, or other medical causes. Conduct medical workup if there are signs of sleep apnea. Sleep hygiene education (e.g. need to wind down before bedtime), increase of daytime activity/exercise, avoidance of caffeine, eating snacks high in tryptophan (e.g. milk, cookies, bananas) before bedtime, and relaxation training.	Before adding a medication for sleep, try to adjust patient's regular medication (e.g. shift the dose of a sedating medication to bedtime). If restlessness is due to an SSRI, give it in the morning, lower the dose, or re-evaluate the patient's medication. If insomnia persists after alternatives are not successful, add a benzodiazepine or zolpidem (Ambien) at bedtime (Grade C). If there is a need to avoid the use of a benzodiazepine or zolpidem because these are addictive or habituating, then trazodone can be used. Be aware that some short-acting sedatives such as zolpidem can cause transient psychotic episodes during the night. Trazodone has been associated with priapism, and male patients should be warned about this rare side effect. Examples of dose ranges: lorazepam 1-2mg, zolpidem 5-10mg, trazodone 25-50mg, benadryl 25-50mg (use antihistamines only if also required to treat EPS and/or if avoiding benzodiazepines is necessary for substance abusing patients). Benzodiazepines are indicated for the short-term treatment of insomnia only. Use flexible or intermittent dosing or prescribe benzodiazepines every second/third night in order to reduce the development of drug tolerance.

NOTE: Benzodiazepine Warning[22]

Avoid ongoing or excessive use of benzodiazepines (no more than 2-3 weeks of continuous use) because of the development of tolerance and withdrawal. Slowly discontinue benzodiazepine if longer term or high dose use occur. Benzodiazepine therapy can result in the following: excessive daytime drowsiness, cognitive impairment and confusion, psychomotor impairment and risk of falls in the elderly, paradoxical reactions (behavioral disinhibition) and depression, amnestic syndromes, respiratory problems, abuse and dependence, and breakthrough withdrawal reactions.

ANTIPSYCHOTICS AND DOSING

These are general recommendations about starting patients on APs and establishing a therapeutic dose. Evidence suggests that some patients may not respond until they receive a dose above the range recommended in the drug labeling, although most patients will respond to drugs in the recommended range. Refer to Prescribing Information for further details.

DOSING OF ATYPICAL APs	
Aripiprazole	Starting dose is 10 or 15 mg given once daily, and this is the usual maintenance dose. Drug has been used in doses up to 30 mg/day in trials.
Clozapine	Recommended starting dose is 12.5 mg (half of a 25 mg tablet) on day one. If this does not produce symptomatic postural hypotension, the patient should receive 25 mg at bedtime for 3 days. Further increases at the rate of 25 mg every 3 days can be given, if tolerated. Above 100 mg/day, dose increases can be by 50 mg every 3 days until a daily total dose of at least 300 mg is reached. Dose range is 200-900 mg/day (200-600 preferred) in divided doses.
Olanzapine	Can usually be adjusted in 5 mg increments every 7 days, after a starting dose of 10 mg/day. Average daily dose is about 15 mg/day, but some patients may not respond until doses of 20 mg or higher. Can be taken at bedtime.

DOSING OF ATYPICAL APs	
Quetiapine	Started at 25-50 mg twice a day. Titrated to at least 300 mg (150 mg bid) over 3-7 days (patients may have postural hypotension and sedation that is mild and will improve with time.) Probably needs to be given twice daily in a dose up to 800 mg/day.
Risperidone	Doses are usually adjusted in 1-2 mg increments every 3-7 days. Most patients respond to an average daily dose of 4-5 mg once a day.
Ziprasidone	Usually given at an initial dose of 40-80 mg/day. Can be titrated up to 120-160 mg/day (target dose over 3-7 days). Maximum dose is 160 mg/day, and this can eventually be given as one bedtime dose.

CHOICE OF AP MEDICATION IN THE ACUTE PHASE OF TREATMENT	
First Episode	Use a low dose of an atypical
Persistent suicidal ideation or behavior	Use clozapine
Persistent hostility or aggression	Use clozapine
Presence of Tardive Dyskinesia	Use atypical AP to avoid further exacerbation of T.D., and use clozapine if severe T.D.
History of EPS	Use atypicals, except for high dose risperidone
History of weight gain, hyperglycemia, hyperlipidemia	Use ziprasidone or aripiprazole
Non-adherence	Use depot AP agents

Adjust Dosage Based on Age, Gender, Race, and Ethnicity[23]

For elderly patients, starting and optimal doses are generally one-quarter to one-half of adult doses. Age related physiological changes alter the adsorption, distribution, metabolism, and excretions of medications and may result in prolonged drug effects and greater sensitivity in terms of both side effects and therapeutic effects. Elderly patients and those with dementia are at high risk for tardive dyskinesia.

There are racial/ethnic differences in metabolism. Asians respond to lower doses of APs and develop toxic side effects at lower doses than do Whites (due to increased blood levels). No known pharmacokinetic differences exist between Whites and African-Americans. However, it is reported that up to one-third of African Americans may have genetic polymorphisms of enzymes that metabolize psychotropic agents, resulting in altered metabolism that can cause more adverse effects.

Women generally require lower dosages than men, and further dose adjustments may be necessary during pregnancy, when symptoms of schizophrenia may be somewhat less. See also Side Effects During Pregnancy, p.35.

MANAGEMENT OF RESIDUAL SYMPTOMS AND CO-MORBID CONDITIONS

RESIDUAL POSITIVE OR AFFECTIVE SYMPTOMS[24]

Assessment / Non-pharmacological Management	Pharmacological Management
The presence of hallucinations, delusions, suspiciousness, disorganization or hypomania/mood lability should be carefully assessed and then documented.	Optimize AP dose, or Consider use of a mood stabilizer (Grade C). If no response, advance to next step of the treatment sequence.

RESIDUAL NEGATIVE SYMPTOMS[25]

Assessment / Non-pharmacological Management	Pharmacological Management
Prolonged response time, unchanging facial expression and flatness, reduced social drive, and poor grooming/hygiene should be carefully assessed and documented. Rule out depression and akinesia.	Decrease conventional AP dose, or Add an SSRI (Grade C). If no response, switch to an atypical AP or go to the next step in the treatment sequence.

CATATONIA[26]

Assessment Non-pharmacological Management	Pharmacological Management
Characterized by either motor excitement or by prolonged immobility/waxy flexibility/posturing, grimacing, and mutism. May alternate with excitement and hyperactivity. Rule out residual catatonic state following Neuroleptic Malignant Syndrome.	Benzodiazepines, especially lorazepam IM, are effective in inducing temporary remission of "functional" catatonia. Continue benzodiazepines po until catatonic symptoms abate and/or the underlying cause is addressed. Consider ECT if clinical emergency.

PERSISTENT AGITATION OR AGGRESSION[27]

Assessment / Non-pharmacological Management	Pharmacological Management
Make differential diagnosis or determine underlying cause of aggression: Internal psychotic stimuli (delusions or hallucinations) Akathisia Physical problems that may be exacerbating behavior Neurological basis Affective disorder	Increase AP dose to treat psychosis, or decrease dose if EPS occurs. When aggressiveness is associated with impulsivity or manic-like symptoms, consider adding lithium, carbamazepine, valproate, or other mood stabilizers; however, evidence for effectiveness of these agents in individuals with schizophrenia is weak, especially for use longer-term (Grade C), and these agents can affect AP blood levels.[28] If there is no response after an adequate mood stabilizer trial, consider going to the next step in the treatment sequence or switch to clozapine, which has shown greater effectiveness than other APs in reducing hostility and aggression (Grade B).[29]
Use behavioral management and cognitive behavioral therapies, including anger management.	Consider use of propranolol or a centrally acting beta-blocker, especially if treating agitation in the neurologically impaired (Grade B).[30] Note that beta-blockers increase blood levels of many APs. Usual Propranolol dose 180–800 mg/day. Start with 20 mg t.i.d and increase by 60 mg q 3 days (up to 12 mg/Kg or until agitation diminishes). This requires careful monitoring of vital signs.

ANXIETY

Assessment / Non-pharmacological Management	Pharmacological Management
Rule out akathisia and caffeine use. Diagnose specific anxiety disorders (e.g., PTSD or panic disorder).	Prescribe a benzodiazepine, propranolol, or an antidepressant (Grade B). Avoid continuous use of benzodiazepines for more than 2-3 weeks to avoid development of tolerance.[31]

OBSESSIVE COMPULSIVE SYMPTOMS[32]

Assessment / Non-pharmacological Management	Pharmacological Management
Evaluate and document intrusive thoughts, repetitive behaviors and rituals, etc.	Consider switching to a more sedating AP. Clozapine, olanzapine and risperidone rarely may precipitate obsessive compulsive symptoms in some patients. If intractable and DSM IV criteria for OCD are met, add an SSRI or clomipramine (Anafranil) (Grade C).

WARNING

Some patients will become more agitated with the use of tricyclics or will develop akathisia from SSRIs.

Avoid bupropion, fluoxetine or fluvoxamine with clozapine. Monitor clozapine levels when using an SSRI or other antidepressants because of their ability to inhibit cytochromeP450 enzymes and increase clozapine levels.

COGNITIVE DEFICITS

Assessment / Non-pharmacological Management	Pharmacological Management
Evaluate mental status carefully. Use a rating tool (such as the Mini-Mental State Exam, or MMSE) to document degree of impairment. Assess whether the patient's medication regimen may be contributing to impairment.	Discontinue anticholinergics and other medication that may be causative. If the patient is on a conventional AP, switch to an atypical agent that is less likely to cause impairment (Grade C).[33]

DEPRESSION

Assessment / Non-pharmacological Management	Pharmacological Management
Rule out reactive depression (the result of situational problems that will respond to supportive therapy and psychosocial interventions). Negative symptoms (sleep disturbance, concentration problems, and anhedonia), sedative or parkinsonian side effects can mimic depression. Make differential diagnosis of depression by the presence of signs like diurnal mood variation, guilt, early morning awakening or terminal insomnia, etc.	Try to adjust the AP dose first before adding another agent. If the patient is acutely psychotic, increase the dose to treat symptoms. If the patient has akinesia or parkinsonian side effects, decrease the dose. Clozapine has some antidepressant effects in schizophrenia (Grade C) and should be considered if antidepressants cannot be used. Clozapine is the only AP that has an indication for effectiveness in preventing suicide.[34] If psychotic symptoms are adequately treated and DSM IV criteria for a major depressive episode are met, add an antidepressant (Grade C). There is limited evidence for the effectiveness of antidepressants in depressed individuals with schizophrenia.[35]

Assessment / Non-pharmacological Management	Pharmacological Management
Use a rating tool (Beck, Hamilton, etc) to monitor symptom severity. Assess for suicide risk. Consider that, when compared to the general population, individuals with schizophrenia are about nine times more likely to commit suicide.	
Build self-esteem and confidence with psychosocial treatment and individual therapy, including cognitive behavioral therapy.	**WARNING** Some patients will become more agitated with the use of tricyclics or will develop akathisia from SSRIs. Avoid bupropion, fluoxetine or fluvoxamine with clozapine. Monitor clozapine levels when using an SSRI or other antidepressants because of their ability to inhibit cytochromeP450 enzymes and increase clozapine levels.

SUBSTANCE ABUSE[36]

Assessment / Non-pharmacological Management	Pharmacological Management
Conduct substance abuse assessment, using collateral reports (family members, providers, etc.) when available. Evaluate medical consequences of abuse. Consider that substance abuse is an indicator of potential medication non-adherence. No specific pharmacological treatments exist for substance abuse. Avoid benzodiazepines or other drugs that can be abused. Provide education; relapse prevention counseling; 12-step programs; cognitive behavioral interventions; referral to a MICA program or structured living situation.	

PSYCHOSIS-INDUCED POLYDIPSIA (POLYDIPSIA/ HYPONATREMIA)[37]

Assessment / Non-pharmacological Management	Pharmacological Management
Diagnosis of hyponatremia is made when fluid intake is excessive (over 1000cc per day) and serum sodium is 125mEq/l or less. Signs: anorexia, nausea, vomiting, difficulty concentrating, confusion, lethargy, agitation, headaches and seizures. Rule out underlying medical causes of hyponatremia: SIADH, Addisons disease, diabetes, excess NaCl loss (as with severe diarrhea and vomiting), renal disease. Development of hyponatremia has been associated with the use of diuretics, SSRIs, tricyclic antidepressants, and calcium antagonists.	Consider switching to clozapine (Grade B), although longer-term effectiveness is not known. Some small studies recommend use of propranolol in patients with polydipsia (Grade C). Other work is being done on Atypical APs, demeclocycline, naltrexone, enalapril, and clonidine. Restrict fluids and provide supportive medical treatment. Sodium replacement to prevent seizures. **Target Weight** procedure allows monitoring of at-risk individuals. Requires twice daily weight measurements (morning and evening). When weight exceeds established target, restrict fluids and do a stat serum sodium level.

INADEQUATE RESPONSE WORK-UP[38]

In the event that a poor response is exhibited, follow the steps listed below before another AP trial is initiated.

Consider whether non-adherence is a factor.

Evaluate pharmacokinetic issues, and use blood level monitoring, when available. Some patients are rapid metabolizers or have pharmacokinetic drug interactions or a metabolic condition that affects their blood levels.

Consider whether psychosocial stressors or past trauma could be interfering with the patient's response.

Rule out ongoing substance use (urine drug testing).

Consider whether unseen side effects may be present and affecting response.

Conduct a medical examination and laboratory testing to consider whether an undiagnosed or uncorrected medical condition may be present.

Re-evaluate psychiatric diagnosis. Consider conducting a structured interview (SCID), psychological testing, or obtaining a consultation for another opinion.

Review adequacy of prior antipsychotic trials and their outcomes.

ECT USE IN SCHIZOPHRENIA[39]

ECT in combination with antipsychotic agents should be considered for patients with severe psychotic symptoms that have not responded to clozapine or other antipsychotics. The efficacy of ECT in schizophrenia has been demonstrated in a number of controlled studies, especially in patients with catatonia, treatment resistant co-morbid depression, and/or suicide ideation. Special consideration should be given to obtaining informed consent.

ASSESSMENT AND MANAGEMENT OF NON-ADHERENCE[40]

WHEN TO ASSESS ADHERENCE

Assess adherence throughout the course of treatment. Patients with schizophrenia often stop taking medications, and choose not to participate in recommended treatments. Partial adherence is common; missing doses and taking 'drug holidays' are general types of partial adherence.

Risk factors for non-adherence include: lack of insight, lack of a therapeutic alliance, discrimination associated with the illness, cultural beliefs, failure to understand the need to take daily medication even if asymptomatic, cognitive impairment, experience of unpleasant medication side effects, substance use, complex medication regimens, chronic conditions, difficulty recognizing symptoms and poor family involvement/supports.

HOW TO ASSESS ADHERENCE

Obtain an adherence history. Ask patients, their family and/or significant others about past practices. Acknowledge that discussing missed doses is difficult.

How patients are asked about adherence affects response. Ask the patient and family about adherence in a non-judgmental way. For example, ask "do you have trouble remembering to take your medications?" rather than "do you take your medication?" Go from general questions, such as "how did it go this week?" to specific, such as "when did you take your medication yesterday?"

Assess the *patient's* perception of the benefits of treatment, the risk of illness, and cost (drowsiness, sexual dysfunction, weight gain) of treatment. The real question is whether or not the patient believes that the medication is effective, and whether or not the patient believes the side effects are tolerable. Patients are unlikely to adhere to treatment if they do not believe they need it.

Assess adherence objectively by obtaining blood levels, pill counts, records of prescription pick-up, family observation.

Observe patient response or lack of response to medication; as well as patient side effects, or lack of side effects. Studies show that clinicians who rely only on patient report overestimate adherence.

HOW TO SUPPORT ADHERENCE

Integrate the patient's family/significant others in treatment planning and education to the greatest possible extent.

Recognize attitudes and behaviors with respect to medication rather than taking a general psycho-educational approach. Most patients have some ambivalence about taking antipsychotic medications and may not perceive their prescribed medication as potentially or actually helpful. Assist the patient to identify reasons to take medication, help them see there is something in it for them.

Use motivational and cognitive behavior techniques to enhance insight and treatment adherence. Help the patient link the medication to goals and aspirations. For example, if the patient's long term goal is getting a part time job, help the patient see how the medication can help him achieve that goal; (less confusion, etc). Identify short term goals as well; for example, making dinner for family, attending a self group, etc.

Use behavioral tailoring and reminders by linking medication taking to other activities (e.g. brushing teeth, going to bed, etc.), or by pill boxes with alarms, particularly for individuals with cognitive deficits (poor memory, confusion).

Empower patients to control their treatment to the greatest degree possible. For example, collaborate on medication adjustments, and incorporate self medication programs.

Simplify the medication regimen by reducing the number of pills and ordering medications to be taken once, or as few times as possible, daily. Most APs can be given as a single dose. **Consider medications with longer elimination half-life to improve adherence**. Patients who are prone to forget doses or are intermittently non-adherent may require drugs with a slower rate of metabolism.

Explain side effects to the patient. Expected/transient side effects may be more tolerable than unexpected ones that last for an unknown duration. Studies support that informing patients about side effects, even tardive dyskinesia, leads to better long term adherence because it reduces patient fear and increases trust in the clinician.

Encourage patients to report side effects and attempt to diminish or eliminate them. Patients differ considerably in regard to how they experience side effects and to what degree particular side effects bother them.

MAINTENANCE PHASE ISSUES

Maintenance therapy with APs can reduce relapse rates (Grade B).[41] There is no evidence that any one AP is better than another in preventing relapses, although one trial has demonstrated superiority of risperidone to haloperidol (Grade B).[42]

Depot APs may also be more effective than oral agents in preventing relapse in certain individuals who are non-adherent to oral medications (Grade C), but the evidence that these improve long-term relapse is inconclusive.[43]

Patients should be maintained on the lowest effective dose in order to avoid side effects and other untoward reactions. There is no evidence that patients receiving higher dosages (> 600 mg equivalents of chlorpromazine) will have reduced relapse rates. If the patient has been receiving high dose AP therapy, an attempt should be made to gradually lower the dose (Grade B).[44]

Goals of the maintenance phase include addressing any breakthrough symptoms and encouraging adherence to medication in order to reduce relapse.

DURATION OF AP MAINTENANCE THERAPY[45]

In first break/single episode patients with a rapid onset of psychosis and full remission, APs can be discontinued after a minimum treatment of 9-12 months in order to avoid long-term side effects (Grade C).

When patients have had multiple episodes but have shown complete remission of symptoms over at least 2-3 years of treatment, consider a slow taper and discontinuation of medication over several months.

When patients have had multiple episodes and show incomplete remission or have a history of serious violence to self or others when not treated, they should receive maintenance AP therapy (Grade B).

Note: Any decisions regarding the duration of AP therapy should be made collaboratively with patients and take into consideration their experiences with side effects and other factors. The above guidelines are based on research studies and primarily look at issues of relapse.

MANAGEMENT OF BREAKTHROUGH SYMPTOMS[46]

When psychotic symptoms reappear, the first step is to assess any potential precipitants. Patients who demonstrate breakthrough symptoms may be reacting to external stressors rather than experiencing decreased response to AP medications.

Studies suggest that patients on long-term maintenance are unlikely to respond to an increase in dose when breakthrough symptoms occur, and increases in AP medication, if needed, should be necessary only for a short period (Grade C).

Address medication side effects as a cause for relapse if there is the possibility that this is a factor, especially if there are drug interactions that are causing side effects from increased blood levels.

EVALUATION AND MANAGEMENT OF SIDE EFFECTS[47]

(also see Monitoring and Laboratory Testing Guidelines)

EXTRAPYRAMIDAL / CNS SIDE EFFECTS[48]

Side Effect	Treatment Options
Dystonia	Add an anticholinergic
Acute rigidity	Other options: Switch to atypical AP
Muscle cramping	Use another anticholinergic (Benadryl) or a dopamine agonist (amantadine/Symmetrel)
Parkinsonism	Decrease AP dose or add an anticholinergic
Rigidity, Bradykinesia Tremor,	Other options: Switch to atypical AP
Mask-like facies	Consider another anticholinergic (hydroxyzine/Benadryl)
Akathisia	Add propranolol or an anticholinergic
Restlessness	Other options: Switch to different/atypical AP
Pacing	Consider other beta-blockers (Metroprolol, Nadolol) or benzodiazepines
Tardive Dyskinesia (T.D.) Late-onset dyskinesia (writhing movements, usually of tongue, mouth, lips) and dystonic symptoms	Conduct neurological evaluation and R/O acute EPS, other movement disorders/stereotypical mannerisms similar to T.D. Once T.D. diagnosis is made, conduct risk-benefit assessment on the need for further AP treatment and obtain patient/family consent if need to continue therapy

Side Effect	Treatment Options
T.D. criteria on AIMS+:	List diagnosis as Neuroleptic-Induced Tardive Dyskinesia (333.82) on Axis III
Score of 3 or more in any one body area tested OR score of 2 or more on any two body areas tested,	If early T.D., reduce dose of AP and monitor closely with more frequent AIMS+EPS
AND	If T.D. has progressed, stop AP or reduce dose of AP; switch to clozapine (Grade B); if clozapine cannot be tolerated, use another atypical AP (Grade C)[49]
AP use for 3 months or more	Other options: Add a benzodiazepine, buspirone, Vitamin E, melatonin or food supplement with amino acids (inconclusive evidence that any of these ameliorate T.D)[50]
Neuroleptic Malignant Syndrome (NMS)	R/O sepsis, heat stroke, anticholinergic toxicity, malignant hyperthermia and serotonin syndrome
Autonomic dysregulation (fever, high/labile BP, tachycardia)	Discontinue AP and transfer to general hospital
Rigidity, mutism, staring, tremulousness, and abnormal lab profile (elevated CPK, leukocytosis, BUN/Creatinine, etc)	Wait at least two symptom-free weeks before re-challenging, then use different AP; select AP that has been safely prescribed in past and/or clozapine, or another atypical AP, or use low potency conventional AP (Grade C). Avoid I.M. medication. Obtain consent. Continue to monitor vital signs, CPK and WBCs when re-challenging.[51]
Heat-Related	Cooling and hydration
Heat stroke, heat cramps	Patient education to prevent further episodes
	Emergency medical management for heat stroke

Side Effect	Treatment Options
Sedation	Give medication at bedtime Monitor thyroid Other options: Switch to less sedating AP
Seizures	Consult with neurologist Add anticonvulsant Other options: Switch to different AP

SYSTEMIC/METABOLIC EFFECTS[52]

Symptom	First Line Treatment Option	Other Options
Dry Mouth	Sugarless hard candy/gum D/C or decrease dose of anticholinergics	
Constipation	High fiber diet, bulk laxative, fluids D/C or decrease dose of anticholinergics	
Urinary Hesitancy	D/C or decrease dose of anticholinergics	Urology consultation
Postural Hypotension Syncope/dizziness	Education (e.g. sitting awhile before rising from bed) Hydration/support hose Switch to high potency AP	Add salt-retaining steroid after medical consultation
Visual problems Blurred vision, increased intraocular pressure, Pigmentary retinopathy	Decrease AP dose D/C the AP or any anticholinergics R/O lenticular opacities with quetiapine	Ophthalmologic consultation

Symptom	First Line Treatment Option	Other Options
Hypersalivation[53]	Dosage reduction (especially clozapine) Check for esophageal dysfunction Sugarless gum (assists swallowing)	Add anticholinergic or clonidine 0.1-0.3 mg bid (can also use patch applied weekly)
Enuresis	Reduce/divide dosage (especially clozapine) with larger dose in AM	Medical consultation
Amenorrhea or Galactorrhea	Decrease dose or change AP Gyn consultation/ Pregnancy Test	Prolactin level
Sexual dysfunction[54] Orgasmic dysfunction, Erectile problems, etc.	Decrease dose or switch to another AP	Prolactin level
Osteoporosis	Use AP with minimal to no effects on prolactin	
Skin Rash	D/C or switch AP	Dermatology consultation
Photosensitivity Severe sunburn	Education, clothing (broad-rimmed hat and long sleeves), and sunblock use	Switch AP
Glucose Intolerance[55]	Switch to another AP	Monitor fasting glucose

Symptom	First Line Treatment Option	Other Options
Weight gain[56]	Patient education and exercise Nutritional consultation/regular weights Switch to AP less likely to cause weight gain (molindone, ziprasidone)	Add appetite suppressant Medical consultation Behavioral training to control excess caloric intake
Tachycardia	Lower AP dose (tolerance develops with clozapine use within 3 to 4 weeks)	Switch to high potency AP
EKG Changes/ Cardiac Effects[57] Prolonged QT, torsade de pointes, myocarditis, thrombosis/ embolism	Change AP Avoid low potency APs, ziprasidone, or possibly aripiprazole	Medical consultation
Hematological Leukopenia or agranulocytosis	Repeat tests and monitor carefully Stop AP	If fever/other symptoms persist, medical consult, antibiotics, supportive care
Liver Dysfunction[58]	Repeat tests and monitor carefully Switch or stop AP	Medical consultation
Withdrawal Reaction[59] Nausea, vomiting, sweating, irritability and headache	Supportive treatment. Prevent by slow cross-taper (clozapine produces more severe reaction that includes rebound psychosis)	
Dysphoria/ Behavioral Toxicity	Switch to another AP	Add an antidepressant

Symptom	First Line Treatment Option	Other Options
Pain at Injection Site of Depot AP	Switch to another depot AP (depot haloperidol may be less painful than depot fluphenazine)[60]	

SIDE EFFECTS DURING PREGNANCY[61]

Because of the potential for teratogenesis and other adverse events in the fetus or newborn, use APs only when benefits outweigh the risks (especially avoid use in the first trimester). Consider patient's severity of illness, efficacy and toxicity of available drugs, anticipated response of the mother (and fetus) when prescribing APs.

Avoid depot agents, clozapine and low potency APs (these present with the greatest risk in pregnant woman due to withdrawal effects on fetus).

Dose requirements change during pregnancy. Monitor treatment closely and ensure lowest effective dose of any agent.

When possible, discontinue psychoactive drugs by gradually tapering the dose before estimated delivery date to minimize neonatal effects in the newborn.

Obesity and folate deficiencies have been associated with neural tube defects. Recent recommendations include the prescribing of high dose folate (4 mg daily) to prevent neural tube defects, especially in women on atypical agents.

Restart AP and other medications immediately after delivery, in order to prevent postpartum psychosis.

Warn against breast feeding as APs are excreted in breast milk.

When counseling women of child-bearing age about becoming pregnant, consider that hyperprolactinemia may protect them from becoming pregnant. Resolution of hyperprolactinemia after a switch from risperidone or conventional AP to another AP can increase the risk that they can conceive and require the use of contraceptives.

MONITORING AND LABORATORY TESTING PROTOCOLS FOR APs

AP BLOOD LEVEL MONITORING[62]

Use blood level monitoring, when available, in order to evaluate pharmacokinetic issues. Some patients are rapid metabolizers or have a drug interaction or a metabolic condition that can affect their AP blood levels. The range of blood levels that correspond with toxicity remains unclear and therapeutic blood levels have not been well established. Certain adverse reactions are not dose related, such as hematological and cardiac effects. Therefore, the current literature dose not recommend the testing of AP blood levels in everyday clinical practice. Refer to the therapeutic blood level ranges in the table below.

Indications for obtaining AP Blood Levels

Poor clinical response (e.g., when a patient fails to respond to an adequate AP dose or when a patient's condition changes suddenly on a regularly prescribed dose)

Signs of toxicity (e.g., when there is difficulty distinguishing between AP side effects and symptoms (e.g., akathisia vs. agitation) or when seizures occur in clozpine treated patients)

Drug interactions (e.g., when AP drug/drug interactions may be occurring (e.g. patient's response to medication changes suddenly).

Altered pharmacokinetics (e.g., when pharmacokinetics are significantly altered in the very young, old, or medically ill.

Suspected non-adherence

AP Therapeutic Blood Level Ranges

Agent	Therapeutic Blood Level (ng/ml)
Clozapine	300 to 700
Risperidone	10 to 120
Haloperidol	5 to 20
Fluphenazine	2 to 10
Perphenazine	0.8 to 2.4
Thiothixene	1.0 to 1.5
Trifluoperazine	1.0 to 2.3

Monitoring and Laboratory Testing[63]

Tests should be done	Baseline	Monthly	at 3 months	At 6 months	Annually
Weights	X	X			
BMI	X			X	
CBC	X				X
SMA-12	X				X
Lipid Panel	X				X
Fasting Blood Glucose or HbA1c **(Category A)**	X				X
Fasting Blood Glucose or HbA1c **(Category B)**	X	*	X		
Aims + / EPS	X		X		
Eye Exam (if on Quetiapine)					**
Prolactin level	As needed for menstrual dysfunction, galactorrhea, gynocomastia, sexual dysfunction, or poor libido (women only)				
ECG	As needed if on Ziprasidone, Thioridazine or Mesoridazone, and/or cardiac risk factors are present, Cardiac risk factors are defined as: • QTc prolongation (>450 mSec); • Known heart disease; • History of fainting/palpitations; • Family history of cardiac death at age 40 or below; • Co-therapy drugs with cardiac effects				

Category A = Aripiprazole. Ziprasidone, all conventionals APs
Category B = Clozapine, Olanzapine, Quetiapine, Risperidone
* First month only if diabetic risk factors are present.
** Eye exam for lenticular opacities every two years

Diabetic Risk Factors

- Overweight or weight increase;
- Over age 45;
- Family history of diabetes (first degree relative);
- Sedentary lifestyle;
- Race/ethnicity (African American, Hispanic, Native American, Asian/Pacific Islander;
- Hypertension;
- Hyperlipidemia;
- Hypercholesterolemia;
- History of gestational diabetes or delivery of baby > 9 lbs.

Calculating BMI (Body Mass Index)*

$$\frac{\text{Weight in Pounds x 703}}{\text{Height in Inches Squared}} = \textbf{BMI}$$

$$\frac{\text{Weight in Kilograms}}{\text{Height in Meters Squared}} = \textbf{BMI}$$

BMI Categories**
<18.5 = underweight
18.5-24.9 = normal weight
25-29.9 = overweight
30 or more = obesity

* Center for Disease Control
** National Institute of Health - National Heart, Lung and Blood Institute

MEDICATION INFORMATION TABLES

AP DRUG/FOOD INTERACTIONS

	Mechanism and Clinical Impact
Alcohol	Additive sedation and incoordination (haloperidol may increase alcohol levels)
Antacids	Decreased absorption (chlorpromazine) , therefore give a few hours apart.
Anticholinergics	Additive anticholinergic effects (low potency agents and clozapine). Cognitive impairment, especially in elderly.
Carbamazepine	Induction of P450 enzymes increases drug metabolism and decreases AP levels (aripiprazole, haloperidol and chlorpromazine). Possible bone marrow toxicity with clozapine.
Valproate	Inhibition of P450 enzymes increases AP levels (clozapine). Valproate levels increased by clozapine.
SSRI Antidepressants	Competitive inhibition of microsomal oxidation resulting in possible increase of AP levels (fluvoxamine and fluoxetine cause increase of aripiprazole, clozapine, olanzapine, haloperidol, and thiothixene levels). Possible EPS (fluoxetine).
Bupropion	Significantly increases levels of clozapine, olanzapine, risperidone and phenothiazine.
Tricyclic Antidepressants	Competitive inhibition of microsomal oxidation can increase AP levels (clozapine,haloperidol,etc.). The AP may also increase TCAs to toxic levels, but effects are inconsistent. Can prolong QTc.

	Mechanism and Clinical Impact
Antipsychotics	Avoid concurrent use of ziprasidone, thioridazine, mesoridazine and chlorpromazine because of cardiac effects .
Benzodiazepines	Lorazepam is associated with respiratory arrest if used with clozapine. Alprazolam and buspirone can increase haloperidol levels.
Beta-blockers	Propranolol decreases AP elimination there by increaseing levels (clozapine, haloperidol, thioridazine and thiothixene).
(H2) Antagonists	Inhibition of P450 oxidative metabolism (cimetidine) decreases AP levels, especially of clozapine.
Lithium	Potential neurotoxicity, especially with haloperidol. May increase clozapine levels. Can Prolong QTc.
Nicotine	Decrease levels of antipsychotics (haloperidol, fluphenazine, olanzapine, and clozapine).
Excessive Caffeine	Increases levels of olanzapine and clozapine.
Grapefruit	Inhibition of P450 can increase levels of clozapine, amitriptyline, imipramine, and clomipramine.

ANTIPSYCHOTICS SIDE EFFECT PROFILES[64]

	CONVENTIONALS		ATYPICALS					
Item	Low Potency	High Potency	Aripiprazole	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasidone
EPS	+	+++	+ / ?	0	+ / ++ (IF > 6 mg)	0 / + (if > 10 mg)	0	0 / +
Tardive Dyskinesia	++	+++	?	0 / +	+	+	+	+
Seizures	++	+	?	++ / +++ (if > 600 mgs.)	+	+	~+	+
Sedation	+++	+	0 / ?	+++	+	++	++	0 / +
Orthostasis	+++	+ / ++	+ / ?	+++	++	+	++	+ / ++
Cardiac Conduction (QT Prolongation)	++	+ / ++	0 / ?	+ / ++	+	+	+	+++
Increased LFT's	++	++	+/ ?	++	0 / +	++	++	0 / +

	CONVENTIONALS		ATYPICALS					
Item	Low Potency	High Potency	Aripiprazole	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasidone
Anticholinergic	+++	+	0 / ?	+++	0 / +	+	0 / +	0 / +
Prolactin Elevation	++	++ / +++	0 / ?	0 / +	+++	0 / +	0	0 / +
Weight Gain	+++	++ / +	0 / ?	+++	++.	+++	++.	0
Diabetes Exacerbation	+	+ / ++	0 / ?	+++	+	+++	++	0
Hypertriglyceridemia	+	+ / ++	0 / ?	+++	+	+++	++	0
Focal Cataracts	+	0?	?	0?	0?	0?	Some risk	0?

Frequency and severity of side effects: + = Low incidence of side effects
++ = Moderate incidence of side effects
+++ = High incidence of side effects

AVERAGE MONTHLY COST

Drug	Avg Dose (mg)	Dollar Sign
fluphenazine	7.5	$
fhiothixine	20	$
chlorpromazine	450	$
Moban	45	$
haloperidol	8.5	$
thioridizine	450	$$
perphenazine	36	$$
trifluoperazine	22.5	$$
loxapine	45	$$$
Serentil	225	$$$
Risperdal	4	$$$$
Risperdal M	4	$$$$
clozapine	400	$$$$
Geodon	120	$$$$$
Seroquel	450	$$$$$
Abilify	15	$$$$$
Zyprexa	15	$$$$$$
Zyprexa Zydis	15	$$$$$$
Clozaril	400	$$$$$$

PRESCRIBING INFORMATION[65]

ATYPICAL ANTIPSYCHOTICS

Drug	Dosage Forms	Adult Dosing (per day)			Side Effects/ Drug Alerts
Generic/ Brand	Tab/Cap/Liq (mg/ml)	Starting (mg/ml)	Acute (mg/ml)	Maintenance (mg/ml)	
Aripiprazole/ Abilify	5, 10, 15, 20, 30	10 Give as one daily dose	10–30	10–20	To be determined
Clozapine/ Clozaril	25, 100	12.5-50 Give in divided doses	200–900 (200–600 preferred dose)	200-900 (200–600 preferred dose)	Diabetes Mellitus Agranulocytosis* Seizures Weight gain Myocarditis - rare Pulm. Embolism-rare
Risperidone/ Risperdal	0.25, 0.5, 1, 2, 3, 4	1–2 Can give as one/divided dose	2–10 (2-6 preferred dose)	2–10 (2-6 is preferred dose)	EPS > 6mg Weight Gain Diabetes Mellitus Prolactinemia

Drug	Dosage Forms	Adult Dosing (per day)			Side Effects/ Drug Alerts
Generic/ Brand	Tab/Cap/Liq (mg/ml)	Starting (mg/ml)	Acute (mg/ml)	Maintenance (mg/ml)	
Risperidone/ Risperdal M Tab**	0.5, 1, 2	Same as above	Same as above	Same as above	Same as above
Risperidone/ Risperdal Liquid	1 mg/ml (100 ml)	Same as above	Same as above	Same as above	Same as above
Risperidone/ Risperdal Consta	25, 37.5, 50	25mg IM every 2 weeks	25 – 50	Lowest effective dose	Somnolence Akathesia Parkinsonism Weight Gain
Olanzapine/ Zyprexa	2.5, 5, 7.5, 10, 15, 20	5 – 10 one/divided doses	10 – 20+	10 – 20	Diabetes Mellitus Weight Gain
Olanzapine/ Zyprexa Zydis**	5, 10, 15, 20	Same as above	Same as above	Same as above	Same as above

Drug	Dosage Forms	Adult Dosing (per day)			Side Effects/ Drug Alerts
Generic/ Brand	Tab/Cap/Liq (mg/ml)	Starting (mg/ml)	Acute (mg/ml)	Maintenance (mg/ml)	
Olanzapine/ Zyprexa IM	10 (5mg/ml)	5 –10 as a single IM injection	A second injection (up to 10mg) may be administered 2hrs after the first, and a third injection (up to 10mg) may be administered 4hrs after the second	Oral olanzapine treatment should be initiated as soon as clinically appropriate	Hypotension Bradycardia with or without hypotension or syncope Tachycardia
Quetiapine/ Seroquel	25, 100, 200, 300	50–100 divided doses	150–750	150–750	Cataracts Weight Gain
Ziprasidone/ Geodon	20, 40, 60, 80	40–80 one/divided doses	80–160	80-160	Prolonged QT on EKG

* Ashkenazi Jews have a much higher risk for agranulocytosis due to genetic vulnerability.

** Orally disintegrating tablet.

\+ Olanzapine doses of up to 30mg have been recommended in the 2004 American Psychiatric Association practice guidelines.

CONVENTIONAL ANTIPSYCHOTICS

Drug		Dosage Forms			Adult Dosing		Side Effects and Alerts
Generic/ Brand	Tab/Cap (mg)	PO Liq (mg/ml)	PO Liq (mg/5ml)	IM mg/ml	Acute mg/day	Maintenance mg/day	
Chlorpromazine/ Thorazine	10, 25, 50, 100, 200	30, 100	10	25	300–1000	300–600	cataracts, corneal opacity, pigmentary retinopathy, lenticular pigmentation, photosensitivity
Fluphenazine/ Prolixin	1, 2.5, 5, 10	5	2.5	2.5	5–20	5–12	Photosensitivity
Haloperidol/ Haldol	0.5, 1, 2, 5, 10, 20	2	N/A	5	5–20	5–12	EPS
Loxapine/ Loxitane	5, 10, 25, 50	N/A	N/A	N/A	30-100	30-60	Seizure, photosensitivity
Mesoridazine/ Serentil	10, 25, 50, 100	25	N/A	N/A	150-400	150-300	pigmentary retinopathy prolonged QT on EKG photosensitivity
Molindone/ Moban	5, 10, 25, 50, 100	20	N/A	N/A	30-100	30-60	Hepatitis

Drug		Dosage Forms			Adult Dosing		Side Effects and Alerts
Generic/ Brand	Tab/Cap (mg)	PO Liq (mg/ml)	PO Liq (mg/5ml)	IM mg/ml	Acute mg/day	Maintenance mg/day	
Perphenazine/ Trilafon	2 ,4, 8, 16	3.2	16	5	30-100	16-60	Photosensitivity
Thioridazine/ Mellaril	10, 15, 25, 50, 100, 150, 200	30, 100	25, 100	N/A	300-800	300-600	pigmentary retinopathy **prolonged QT on EKG *** photosensitivity
Thiothixene/ Navane	1, 2, 5, 10, 20	5	N/A	N/A	10-50	10-30	lenticular pigmentation
Trifluoperazine/ Stelazine	1, 2, 5, 10	10	N/A	N/A	15-50	15-30	Photosensitivity

* Black box warning

PHARMACOKINETIC PARAMETERS AND DOSING OF DEPOT APS *

Drug	Dosage Form	Conversion from oral dose	Maintenance Dosage	Max Dose per injection	Costs per month
Haloperidol decanoate	50-100 mg/ml	10 to 20 x oral dose	50–200 mg / 4 weeks	200 mg	$$
Fluphenazine decanoate	25 mg/ml	1.2 x oral dose	12.5–37.5 mg / 2-3 weeks	37.5 mg	$

* Patients maintained for 1 year or longer demonstrated a very long time to wash out drug (terminal observed half-life exceeding 60 days).

PHARMACOKINETIC PARAMETERS AND DOSING OF LONG ACTING IM

Drug	Dosage Form	Conversion from oral dose	Maintenance Dosage	Max Dose per injection	Costs per month
Risperidone/ Risperdal Consta	25, 37.5, 50 Intra-muscular	No dose equivalent data at this time	Lowest effective dose	50 mg/ IM every 2 weeks	25mg $$$$ 37.5mg $$$$$ 50mg $$$$$$$

AGENTS FOR AP MOTOR SIDE EFFECTS

	Generic	Brand	Tab/Cap (mg)	PO Liq. (mg/ml)	IM mg/ml	Uses	Typical Dose (mg)
Anticholinergics	**Benztropine**	**Cogentin**	0.5, 1, 2	N/A	1	**dystonia, rigidity, tremor**	2 IM, 1-2 po bid
	Diphenhydramine	Benadryl	25, 50	12.5mg/ml	10, 50	dystonia, rigidity, tremor	25-50 IM, 25-50 bid
	Trihexyphenidyl	Artane	2.5	0.4	N/A	dystonia, rigidity	2-5 bid
Benzodiazepines	Clonazepam	Klonopin	0.5, 1, 2	N/A	N/A	akathisia	0.5-1 bid
	Lorazepam	Ativan	0.5, 1, 2	2 mg/ml	2, 4	akathisia	0.5-1 bid
Beta Blockers (use lipophilic agents only)	**Propranolol**	**Inderal**	10, 20, 40, 60, 80	N/A	N/A	**akathisia**	10-20 tid
	Metroprolol	Lopress or Corgard	50, 100	N/A	N/A	akathisia	50-100 qd
	Nadolol		20,40,80, 120,160	N/A	N/A	akathisia	20-40 qd
Dopamine agonist	Amantadine	Symmetrel	100	10	N/A	akinesia, rigidity	100 bid or tid

* **Bold face** are the treatments of choice for the conditions listed.

USE OF ANTIPARKINSONIAN / ANTICHOLINERGIC AGENTS FOR EPS:[66]

- Consider prophylactic use on a case-by-case basis, taking into account the patient's past history of EPS and his/her preferences, as well as the risk factors for EPS and for T.D. (higher risk in young and muscular males). Consider use if prescribing a depot AP (Grade B). However, should not be necessary when prescribing lower starting doses, making gradual dose titration, and when using atypicals.

- Reduce anticholinergics slowly over weeks or months before discontinuing in order to avoid withdrawal effects. Also, avoid prolonged use of anticholinergic/antiparkinsonian agents, as these have side effects (cognitive effects, memory loss, constipation, dry mouth, blurred vision, etc), especially in the elderly, and have been associated with an increased risk for T.D. (Grade B).

- Use amantidine to avoid the anticholinergic effects. However, this agent has rarely been known to cause exacerbation of psychosis.

ANTIDEPRESSANTS

Generic	Brand	Class	Dosage Forms	Adult Dosing			Side Effects			Monitoring
			Tab/Cap (mg)	Starting Dose (mg/day)	Typical Dose (mg/day)	Max Dose (mg/day)	Ortho - static Hypoten.	Sed	Antichol	Blood Level (ng/ml)
Escitalopram	Lexapro	SSRI	10, 20, (1mg/ml sol)	10	20-Oct	20	0	0	0	N/A
Citalopram	Celexa	SSRI	20, 40, (10mg/5ml sol)	20	20-60	60	0	0	0	N/A
Fluoxetine Generic available	Prozac	SSRI	10, 20, 40 (5 mg/ml liquid) 90 (Prozac weekly)	10-20	20-60	100	+	+	+	72-300
Fluvoxamine	Luvox	SSRI	25, 50, 100	50	50-300	300	+	+	+	N/A

Generic	Brand	Class	Dosage Forms	Adult Dosing			Side Effects			Monitoring
			Tab/Cap (mg)	Starting Dose (mg/day)	Typical Dose (mg/day)	Max Dose (mg/day)	Orthostatic Hypoten.	Sed	Anticol	Blood Level (ng/ml)
Paroxetine	Paxil Paxil CR	SSRI	10, 20, 30, 40 (10 mg/ 5 ml sol)	10-20	20	50	+	+	+	N/A
Sertraline	Zoloft	SSRI	25, 50, 100 (20 mg/ml)	25-50	50-200	200	+	+	++	N/A
Duloxetine	Cymbalta	SS NRI	20,30,60	40-60	40-60	60	0	+	+	N/A
Nefazodone **NOTE:** Black Box Warning	Serzone	SSRI/ 5 HT2 ant	50, 100, 150, 200, 250	50 bid	450-600	600	+	++	+/0	N/A
Bupropion	Well-butrin Well-butrin SR	Atypical	75, 100 100, 150	75 bid/tid	225-300	450	+	+	+	50-100

Generic	Brand	Class	Dosage Forms	Adult Dosing			Side Effects			Monitoring
			Tab/Cap (mg)	Starting Dose (mg/day)	Typical Dose (mg/day)	Max Dose (mg/day)	Orthostatic Hypoten.	Sed	Antichol	Blood Level (ng/ml)
Trazodone	Desyrel	Atypical	50, 100, 150, 300	25-75	200-300	600	++	++++	+	800-1600
Mirtazapine	Remeron	Alpha 2 antag	15, 30, 45	15	30	45	+	+++	+	N/A
Venlafaxine	Effexor	5HT/NE ri	25, 37.5, 50, 75, 150	37.5 bid	150-300	375	+	+	+	N/A
	Effexor XR		37.5, 75, 150							
Amoxapine	Asendin	TCA 2	25, 50, 100, 150	50-150	200-300	600	++	++	+++	150-500
Desipramine	Norpramin	TCA 2	10, 25, 50, 75, 100, 150	10-75	150-200	400	++	++	++	100-250*

Generic	Brand	Class	Dosage Forms	Adult Dosing			Side Effects			Monitor-ing
			Tab/Cap (mg)	Starting Dose (mg/day)	Typical Dose (mg/day)	Max Dose (mg/day)	Ortho - static Hypoten.	Sed	Antich ol	Blood Level (ng/ml)
Nortriptyline	Pamelor	TCA 2	10, 25, 50, 75	10-40	75-100	200	+	++++	++	50-100*
Amitriptyline	Elavil	TCA 3	10, 25, 50, 75, 100, 150	10-751	150-200	450	+++	++++	++++	100-300*
Clomipramine	Anafranil	TCA 3	25, 50, 75	25-75	150-200	500	+++	++++	++++	72-300
Doxepin	Sinequan	TCA 3	10, 25, 50, 75, 100, 150	25-75	15-200	350	+++	++++	+++	100-250
Imipramine	Tofranil	TCA 3	10, 25, 50, 75, 100, 125, 150	10-75	150-200	450	+++	+++	+++	150-450*

Generic	Brand	Class	Dosage Forms	Adult Dosing			Side Effects			Monitoring
			Tab/Cap (mg)	Starting Dose (mg/day)	Typical Dose (mg/day)	Max Dose (mg/day)	Orthostatic Hypoten.	Sed	Antichol	Blood Level (ng/ml)
Phenelzine	Nardil	MAOI	15	15-30	45-90	90	++++	+++	+++	N/A
Tranylcypromine	Parnate	MAOI	10	10-20	30-50	90	++++	+++	+++	N/A

* Refer to Reference Laboratory Values.

Abbreviations: **SR** (slow release) **XR** (extended release)

\+ to ++++ = Active to Strongly Active

MOOD STABILIZERS

Generic	Brand	Tab/Cap (mg/ml)	PO Liq (mg/ml)	Starting Dose	Adult Dosing Titration	Usual Dose (mg/day)	Side Effects	Therapeutic Blood Levels
Lithium Carbonate	Lithobid (sr) Eskalith Eskalith CR	300 300 450	N/A	225, 300 or 450mg bid or tid	225 - 450mg q3-4d	900 - 1800	hypothyroidism, polyuria, renal insufficiency	1.0-1.2 mEq/L (acute mania) 1.08-1.0 mEq/L (bipolar maint.) 0.4-1.0 mEq/L (antidep augmentation.)
Lithium Citrate	Cibalith-S	N/A	1.6 mEq = 60 mg/ml	300mg bid or tid	300mg q3-4d	900-1800	hypothyroidism, polyuria, renal insufficiency	1.0-1.2 mEq/L (acute mania) 0.8-1.0 mEq/L (bipolar maintenance.) 0.4-1.0 mEq/L (antidep augmentation.)
Valproic Acid	Depakene	250	50	250mg bid or tid (or load: 500mg bid)	250-500mg/wk	1000-4250	hepatotoxicity pancreatitis platelet disorders	50-150 µg/ml*

Generic	Brand	Tab/Cap (mg/ml)	PO Liq (mg/ml)	Starting Dose	Adult Dosing Titration	Usual Dose (mg/day)	Side Effects	Therapeutic Blood Levels
Divalproex sodium	Depakote (dr) Depakote ER Depakote Sprinkles	125, 250, 500 250, 500 125	N/A	250mg bid or tid (or load: 500mg bid)	250-500mg/wk	1000-4250	hepatotoxicity pancreatitis platelet disorders	50-150 µg/ ml*
Carbamazepine	Tegretol Tegretol XR Tegretol chew Carbatrol (er)	200 100, 200, 400 100 200, 300	20	100mg bid or tid	200mg/day	300-1200	hepatotoxicity, hyponatremi, bone marrow depressiona	8-12 µg/mi*
Gabapentin	Neurontin (cap) Neurontin (tab)	100, 300, 400 600, 800	50	300mg qd	300mg q1-2d	1600-3600	fatigue	< 10 ng/mi
Lamotrigine	Lamictal Lamictal (chew)	25, 100, 150, 200 2, 5, 25	N/A	50mg qd x 2 wks	50mg bid q 2 wks	150-500	ataxia, somnolence, rash	N/A

Generic	Brand	Tab/Cap (mg/ml)	PO Liq (mg/ml)	Starting Dose	Adult Dosing Titration	Usual Dose (mg/day)	Side Effects	Therapeutic Blood Levels
Topiramate	Topamax Topamax, Sprinkles	25, 100, 200 15, 25	N/A	12.5-25mg qd or bid	12.5-25mg /wk	100-400	CNS effects	N/A
Oxcarbaze-pine	Trileptal	150, 300, 600	300mg/5 ml	300mg bid	300mg q 3d	600-2400	hyponatremia dizziness ataxia	N/A
Olanzapine and Fluoxetine	Symbyax	6/25, 6/50, 12/25, 12/50	N/A	6mg/25mg qd	According to efficacy and tolerability	6 to 12mg/ 25 to 50mg	Asthenia, edema, som-nolence, weight gain	N/A

* **Refer to Reference Laboratory Values Abbreviations:** sr = slow release, dr = delayed release, er = extended release, CR = controlled release, S = syrup, ER = extended release, XR = extended release

PROBLEM REPORTING CHECKLIST

Name: _____ Date: _____

Directions : Please go through this list and fill in or check all that apply to you, leaving other boxes blank. This information will help in discussing any physical problems possibly related to medication that you are currently having or have had in the past.

Problem	Currently having this problem (✓ box)	Problem occurred in the past (✓ box)	Describe your experience with this problem : When (e.g., now or in the past)? What happened? How did it affect you? Leave blank if you have not had the problem.	I want to discuss this (✓ box)
Too little energy/fatigue				
Slowness/difficulty with movement				
Restlessness /difficulty sitting still				
Muscle stiffness				
Muscles trembling or shaking				
Increased hunger/putting on weight				
Sleeping too much/tired feeling				
Difficulty sleeping/insomnia				
Dizziness				
Rash or itchy skin				
Palpitations (flutter in chest)				
Passing ou t				
Feeling depressed				
Feeling tense				
Dry mouth				
Blurred vision				
Constipation				
Frequent urination				
Problems with memory				
Problems with concentration				
Changes in menstrual periods				
Sex drive or performance concerns				
Other (please specify):				

I also want to discuss _____

Use back of sheet if more space is needed.

AIMS+EPS EXAMINATION

Directions: For each examination, complete the column under the exam date, indicate diagnoses and initial.
Rate movements at their greatest severity observed, always rating movements seen on activation less than those seen at rest.
0=none 1=minimal or extreme normal 2=mild 3=moderate 4=severe (See reverse for details about conducting the examination)

TARDIVE DYSKINESIA

Date of Exams	__/___/__	__/___/__	__/___/__	__/___/__
Facial: (forehead, eyebrow, periorbital, cheeks) e.g., frowning, blinking, grimacing.	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Lips and Perioral : e.g., puckering, pouting, smacking.....	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Jaw: e.g., biting, clenching, chewing, mouth opening, lateral movement.....	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Tongue: e.g., wormlike or thrusting, movements	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Upper Extremities (arms, wrists, hands, fingers): can be choreic (e.g., rapid and purposeless) and athetoid (e.g., slow and complex). Do not rate tremors.....	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Lower Extremities (legs, knees, ankle, toes) e.g., irregular lateral knee or irregular foot or heel movements.....	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Trunk (neck, shoulders, hips) e.g. rocking, twisting, squirming, or pelvic gyrations.	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Teeth: Indicate if 1) No teeth 2) Problems with Teeth or 3) Problems with Dentures				

EXTRAPYRAMIDAL SIDE EFFECTS

Dystonia e.g., persistent spasms of eyes, face, neck, back.....	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Parkinsonism e.g., slowed movements, shuffling gait, masklike facies, resing tremor.....	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Akathisia e.g., restlessness, pacing, rocking, inability to sit still	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Parkinson Tremor e.g., slow, rhythmic, pill rolling, presen t at rest.....	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Akinesia e.g., decreased motor movements, weakness, decreased movements paresthesias	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Indicate Diagnoses (e.g., None, T.D., Dyskinesia, Pa rkinsonism, Akathisia or Akinesia				
Examiner(s) Names _____ Initials:				
_____				

AIMS+EPS Examination Procedure[67]

Either before or after completing the Examination Procedure, observe the patient unobtrusively, at rest (e.g. in waiting room).

The chair to be used in this examination should be a hard, firm one without arms.

Ask patient whether there is anything in his/her mouth (i.e. gum, candy, etc.), and if there is, to remove it.

Ask patient about the current condition of his/her teeth. Ask patient if he/she wears dentures. Do teeth or dentures bother patient now?

Ask patient whether he/she notices any movements in mouth, face, hands or feet. If yes, ask to describe and to what extent they currently bother patient or interfere with his/her activities.

Have patient sit in chair with hands on knees, legs slightly apart, and feet flat on floor. (Look at entire body for movements while in this position.)

Ask patient to sit with hands hanging unsupported. If male, between legs. If female, and wearing a dress, hanging over knees. (Observe hands and other body areas.)

Ask patient to open mouth. (Observe tongue at rest within mouth.) Do this twice.

Ask patient to protrude tongue. (Observe abnormalities of tongue movement.)

Ask patient to tap thumb, with each finger, as rapidly as possible for 10-15 seconds: separately with right hand, then with left hand. (Observe facial and leg movements.)

Flex and extend patient's left and right arms, one at a time. (Note any rigidity and rate it.)

*10. Ask patient to stand up. (Observe in profile. Observe all body areas again, hips included.)

*11. Ask patient to extend both arms outstretched in front with palms down. (Observe trunk, legs and mouth.)

*12. Have patient walk a few paces, turn, and walk back to chair. (Observe hands and gait.) Do this twice.

* Activated movements

In the past 7 days . . .

SCORE SHEET
for
4-ITEM POSITIVE SYMPTOM RATING SCALE AND BRIEF NEGATIVE SYMPTOM ASSESSMENT

4-Item Positive Symptom Rating Scale

Use each item's anchor points to rate the patient.

1. Suspiciousness	*NA	1	2	3	4	5	6	7	
2. Unusual Thought Content	NA	1	2	3	4	5	6	7	
3. Hallucinations	NA	1	2	3	4	5	6	7	
4. Conceptual Disorganization	NA	1	2	3	4	5	6	7	SCORE: _____

*** NA — not able to be assessed**

4-Item Negative Symptom Rating Scale

Use each item's anchor points to rate the patient.

1. Prolonged Time to Respond	1	2	3	4	5	6	
2. Emotion Unchanging facial expression blank, expressionless face.	1	2	3	4	5	6	
3. Reduced Social Drive	1	2	3	4	5	6	
4. Poor Grooming and Hygiene	1	2	3	4	5	6	SCORE: _____

Source of Information (check all applicable)

_____ Patient
_____ Parents/Relatives
_____ Mental Health Professionals
_____ Chart

Confidence in assessment
____ 1=Not at all – 5=Very confident

Explain here if validity of assessment is questionable:

_____ Symptoms possibly drug-induced
_____ Underreported due to lack of rapport
_____ Underreported due to negative symptoms
_____ Patient uncooperative
_____ Difficult to assess due to formal thought disorder
_____ Other _____

The 4-item PSRS was adapted from the Expanded Version of the BPRS developed by:
Ventura, J.; Lukoff, D.; Nuechterlein, K.H.; Libernian, R.P.; Green, M.F.; and Shaner, A. Manual for the expanded Brief Psychiatric Rating Scale. International Journal of Methods Psychiatry Research, 3:227-244, 1993

The Brief Negative Symptom Asse ssment was adapted from the Negative Symptom Assessment and the Scale for the Assessment of Negative Symptoms developed respectively by:

Alphs and Summerfelt. The Negative Symptom Assessment: A new instrument to assess negative symptoms of schizophrenia. Psychopharmacology Bulletin, 1989. 25(2): p. 159-163.

Andreason, N. Modified scale for the assessment of negative symptoms. NIMH treatment strategies in schizophrenia study. Public Health Administration. U.S. Department of Health and Human Services, 1984. ADM (9/85): p. 9-102.

SYMPTOM RATING SCORE SHEET

4-ITEM POSITIVE SYMPTOM RATING SCALE (VERSION 5.0)

SCALE ITEMS AND ANCHOR POINTS

1. **SUSPICIOUSNESS:** Expressed or apparent belief that other persons have acted maliciously or with discriminatory intent. Include persecution by supernatural or other nonhuman agencies (e.g., the devil). Note: Ratings of "3" or above should also be rated under Unusual Thought Content.

   Do you ever feel uncomfortable in public? Does it seem as though others are watching you?
   Are you concerned about anyone's intentions toward you?
   Is anyone going out of their way to give you a hard time, or trying to hurt you? Do you feel in any danger?

   [If patient reports any persecutory ideas/delusions, ask the following]:

   How often have you been concerned that [use patient's description]?
   Have you told anyone about these experiences?

   1 Not Present

   2 Very Mild
   Seems on guard. Reluctant to respond to some "personal" questions. Reports being overly self-conscious in public.

   3 Mild
   Describes incidents in which others have harmed or wanted to harm him/her that sound plausible. Patient feels as if others are watching, laughing, or criticizing him/her in public, but this occurs only occasionally or rarely. Little or no preoccupation.

   4 Moderate
   Says others are talking about him/her maliciously, have negative intentions, or may harm him/her. Beyond the likelihood of plausibility, but not delusional. Incidents of suspected persecution occur occasionally (less than once per week) with some preoccupation.

   5 Moderately Severe
   Same as 4, but incidents occur frequently, such as more than once per week. Patient is moderately preoccupied with ideas of persecu-

tion OR patient reports persecutory delusions expressed with much doubt (e.g., partial delusion).

6 Severe
Delusional – speaks of Mafia plots, the FBI, or others poisoning his/her food, persecution by supernatural forces.

7 Extremely Severe
Same as 6, but the beliefs are bizarre or more preoccupying. Patient tends to disclose or act on persecutory delusions.

2. UNUSUAL THOUGHT CONTENT: Unusual, odd, strange or bizarre thought content. Rate the degree of unusualness, not the degree of disorganization of speech. Delusions are patently absurd, clearly false or bizarre ideas that are expressed with full conviction. Consider the patient to have full conviction if he/she has acted as though the delusional belief were true. Ideas of reference/persecution can be differentiated from delusions in that ideas are expressed with much doubt and contain more elements of reality. Include thought insertion, withdrawal and broadcast. Include grandiose, somatic and persecutory delusions even if rated elsewhere. Note: If Somatic Concern, Guilt, Suspiciousness, or Grandiosity are rated "6" or "7" due to delusions, then Unusual Thought Content must be rated a "4" or above.

Have you been receiving any special messages from people or from the way things are arranged around you? Have you seen any references to yourself on TV or in the newspapers?
Can anyone read your mind?
Do you have a special relationship with God?
Is anything like electricity, X-rays, or radio waves affecting you?
Are thoughts put into your head that are not your own?
Have you felt that you were under the control of another person or force?

[If patient reports any odd ideas/delusions, ask the following]:

How often do you think about [use patient's description]?
Have you told anyone about these experiences? How do you explain the things that have been happening [specify]?

1 Not Present

2 Very Mild
Ideas of reference (people may stare or may laugh at him), ideas of persecution (people may mistreat him). Unusual beliefs in psychic powers, spirits, UFOs, or unrealistic beliefs in one's own abilities. Not strongly held. Some doubt.

3 Mild
Same as 2, but degree of reality distortion is more severe as indicated by highly unusual ideas or greater conviction. Content may be typical of delusions (even bizarre), but without full conviction. The delusion does not seem to have fully formed, but is considered as one possible explanation for an unusual experience.

4 Moderate
Delusion present but no preoccupation or functional impairment. May be an encapsulated delusion or a firmly endorsed absurd belief about past delusional circumstances.

5 Moderately Severe
Full delusion(s) present with some preoccupation OR some areas of functioning disrupted by delusional thinking.

6 Severe
Full delusion(s) present with much preoccupation OR many areas of functioning are disrupted by delusional thinking.

7 Extremely Severe
Full delusions present with almost total preoccupation OR most areas of functioning are disrupted by delusional thinking.

3. HALLUCINATIONS: Reports of perceptual experiences in the absence of relevant external stimuli. When rating degree to which functioning is disrupted by hallucinations, include preoccupation with the content and experience of the hallucinations, as well as functioning disrupted by acting out on the hallucinatory content (e.g., engaging in deviant behavior due to command hallucinations), include "thoughts aloud" ("gedankenlautwerden") or pseudohallucinations (e.g., hears a voice inside head) if a voice quality is present.

Do you ever seem to hear your name being called?
Have you heard any sounds or people talking to you or about you when there has been nobody around? [If hears voices]: What does the voice/voices say? Did it have a voice quality?
Do you ever have visions or see things that others do not see'? What about smell – odors that others do not smell?

[If the patient reports hallucinations, ask the following]:

Have these experiences interfered with your ability to perform your usual activities/work?
How do you explain them? How often do they occur?

1 Not Present

2 Very Mild
While resting or going to sleep, sees visions, smells odors, or hears voices, sounds or whispers in the absence of external stimulation, but no impairment in functioning.

3 Mild
While in a clear state of consciousness, hears a voice calling the subjects name, experiences non-verbal auditory hallucinations (e.g., sounds or whispers), formless visual hallucinations, or has sensory experiences in the presence of a modality – relevant stimulus (e.g., visual illusions) infrequently (e.g., 1-2 times per week) and with no functional impairment.

4 Moderate
Occasional verbal, visual, gustatory, olfactory, or tactile hallucinations with no functional impairment OR non-verbal auditory hallucinations/visual illusions more than infrequently or with impairment.

5 Moderately Severe
Experiences daily hallucinations OR some areas of functioning are disrupted by hallucinations.

6 Severe
Experiences verbal or visual hallucinations several times a day OR many areas of functioning are disrupted by these hallucinations.

7 Extremely Severe
Persistent verbal or visual hallucinations throughout the day OR most areas of functioning are disrupted by these hallucinations.

4. CONCEPTUAL DISORGANIZATION: Degree to which speech is confused, disconnected, vague or disorganized. Rate tangentiality, circumstantiality, sudden topic, shifts, incoherence, derailment, blocking, neologisms, and other speech disorders. Do not rate content of speech.

1 Not Present

2 Very Mild
Peculiar use of words or rambling but speech is comprehensible.

3 Mild
Speech a bit hard to understand or make sense of due to tangentiality, circumstantiality or sudden topic shifts.

4 Moderate
Speech difficult to understand due to tangentiality, circumstantiality, idiosyncratic speech, or topic shifts on many occasions OR 1-2 instances of incoherent phrases.

5 Moderately Severe
Speech difficult to understand due to circumstantiality, tangentiality, neologisms, blocking, or topic shifts most of the time OR 3-5 instances of incoherent phrases.

6 Severe
Speech is incomprehensible due to severe impairments most of the time. Many PSRS items cannot be rated by self-report alone.

7 Extremely Severe
Speech is incomprehensible throughout interview.

BRIEF NEGATIVE SYMPTOM ASSESSMENT SCALE (VERSION 5.0)

Items adapted from NSA and SANS

1. **PROLONGED TIME TO RESPOND** (a measure of Alogia): Observed throughout communication with the patient. After asking the patient a question, he or she pauses for Inappropriately long periods before initiating a response. Delay is considered a pause if it feels as though you are waiting for a response or if you consider repeating the question because it appears that the patient has not heard you. He or she may seem "distant" and sometimes the examiner may wonder if he has even heard the question. Prompting usually indicates that the patient is aware of the question, but has been having difficulty in developing his thoughts in order to make an appropriate reply. Rate severity on the frequency of these pauses.

   1 Normal
   No abnormal pauses before speaking.

   2 Minimal
   Minimal evidence of inappropriate pauses (brief but not abnormally lengthy pauses occur) may be extreme of normal

   3 Mild
   Occasional noticeable pauses before answering questions. Due to the length of the pause, you feel the need to repeat yourself once or twice during the interview.

   4 Moderate
   Distinct pauses occur frequently (20-40% of responses).

   5 Marked
   Distinct pauses occur most of the time (40-80% of responses).

   6 Severe
   Distinct pauses occur with almost every response (80-100% of responses).

2. **EMOTION: UNCHANGING FACIAL EXPRESSION; BLANK, EXPRESSIONLESS FACE** (a measure of Flat Affect): The patient's face appears wooden, mechanical, frozen. Facial musculature is generally ex-

pressionless and unchanging. The patient does not change expression, or change is less than normally expected, as the emotional content of discourse changes. Because of this, emotions may be difficult to infer. Disregard changes in facial expression due to abnormal involuntary movements, such as tics and tardive dyskinesia. The two dimensions of importance when making this rating are degree of emotional expression and spontaneity.

1 Normal
Spontaneous displays of emotion occur when expected. Normal degree of expressiveness of emotions is present.

2 Minimal
Spontaneous expressions of emotion occur when expected. However, there is a reduction in degree or intensity of the emotions expressed. May be extreme of normal.

3 Mild
Spontaneous expressions of emotion occur infrequently. When emotions are expressed there is a reduction in degree or intensity displayed.

4 Moderate
Obvious reduction in spontaneous expressions. Spontaneous expressions of emotion may occur very rarely during interaction and only when discussing topics of special interest or humor to the subject.

5 Marked
Facial expression is markedly decreased. There are no spontaneous expressions of emotion unless prompted or coaxed by the interviewer.

6 Severe
There are no expressions of emotion even when attempts are made to elicit an emotional response. The subject's face remains blank throughout the interview.

3. REDUCED SOCIAL DRIVE. (a measure of Asociality): This item assesses how much the subject desires to initiate social interactions. Desire may be measured in part by the number of actual or attempted social contacts with

others. If the patient has frequent contact with someone (e.g., family member) who initiates the contact, does the patient appear to desire the contact (i.e., would he or she initiate contact if necessary?)? In making this rating, probe the desire to initiate social interactions, number of social interactions and the ability to enjoy them.

Assessed by asking the patient questions like:

How have you spent your time in the past week?
Do you live alone or with someone else?
Do you like to be around people?
Do you spend much time with others?
Do you have difficulty feeling close to others?
Who are your friends?
How often do you see them?
Did you see them this past week?
Have you called them on the phone?
When you get together, who decides what to do and where to go?
When you spend time with others, do you ask them to do something with you or do you wait until they ask you to do something?
Is anyone concerned about your happiness or well being?

1 Normal
Normal desire to initiate and normal number of contacts. Social contacts are enjoyable.

2 Minimal
Minimal reduction in either the desire to initiate social contacts or the number of social relationships. May initially seem guarded, but has the ability to establish relationships over time. Social relationships are enjoyable.

3 Mild
Reduction in desire to initiate social contacts. The patient has few social relationships and these social contacts are enjoyable.

4 Moderate
Obvious reduction in the desire to initiate social contacts. The patient has few relationships toward which he or she feels indifference. However, a number of social contacts are initiated each week.

5 Marked
Marked reduction in desire to initiate social contacts. The patient has very few relationships toward which he or she feels indifference. The patient does not initiate social contacts but may maintain a few contacts (such as with family).

6 Severe
Patient does not desire social contact. Actively avoids social interactions.

4. **GROOMING AND HYGIENE** (a measure of Amotivation): Observed during interaction with the patient. The patient displays less attention to grooming and hygiene than normal. The patient presents with poorly groomed hair, disheveled clothing, etc. Do not rate grooming as poor if it is simply done in what one might consider poor taste (e.g., wild hairdo or excessive makeup). In addition to observation, one must ask the patient about regularity of bathing, brushing teeth, changing clothes, etc. This is particularly important with outpatients, as the patient may present his or her best grooming and hygiene at their clinic visit. Two dimensions to keep in mind when making this rating are current appearance and regularity of grooming behaviors.

Assess the patient by asking questions like:

How many-times in the past week have you taken a shower or bath?
How often do you change your clothes?
How often do you shower and brush your teeth?

1 Normal
Patient is clean (e.g., showers every day) and dressed neatly.

2 Minimal
Minimal reduction in grooming and hygiene, may be at the extreme end of the normal range.

3 Mild
Apparently clean but untidy appearance. Clothing may be mismatched. Patient may shower less often than every other day, or may brush teeth less than everyday.

4 Moderate
There is an obvious reduction in grooming and hygiene. Clothes may appear unkempt, rumpled, or the patient may look as if he or she just got out of bed. The patient may to without shower or bathing for two days at a time. The patient may go for two days without brushing their teeth.

5 Marked
There is a marked reduction in grooming and hygiene. Clothing may appear dirty, stained or very unkempt. The subject may have greasy hair or a body odor. The patient may go 3 days at a time without showering or 3 or 4 days without brushing their teeth.

6 Severe
Clothing is badly soiled. Patient has a foul odor. Patient may go more than 4 days in a row without showering or more than 4 days in a row without brushing his/her teeth. Poor hygiene may present a health risk.

Endnotes

1 For a discussion of the benefits of clinical practice guidelines, see references 1-3.

2 The DMHS Guidelines will be used as a training resource and will also be the focus of drug use evaluation studies and of consultant pharmacist monitoring.

3 See references 4-13 for the practice guidelines reviewed by the workgroup.

4 With the exception of the practice guidelines from the APA and the PORT guidelines, the published practice guidelines currently available are based largely on expert opinion and/or do not provide any citations for the empirical basis of their recommendations.

5 This classification of evidence is based on that used in the PORT guidelines and the Agency for Healthcare Policy Research (AHCPR) depression guidelines. The format is comparable to that of the APA guidelines (reference 3).

6 All of the available practice guidelines (references 4-16) recommend that preference be given to first using the atypical antipsychotics instead of the conventional agents, essentially because the atypical agents produce fewer side effects and individuals generally are better able to tolerate their use.

7 While atypical agents are generally better tolerated than conventional agents, except for clozapine, the atypicals have not been shown to be more effective. Some studies have demonstrated that atypicals may be more effective than conventional agents in treating negative symptoms. However, the empirical evidence suggests that the agents may only be more effective in reducing secondary negative symptoms. Primary negative symptoms correlate with the deficit syndrome of schizophrenia, while secondary negative symptoms may be due to a variety of causes, including EPS side effects, psychotic dysphoria, and a lack of environmental stimulation. Of the

atypicals and other psychotropics currently available, clozapine is probably the most effective treatment for negative symptoms (references 9, 17-23).

8 Because of the overwhelming evidence that supports antipsychotic monotherapy, all of the published practice guidelines make this recommendation. Dosage should be in the recommended ranges (generally between 300-1000 mg equivalents of chlorpromazine). Refer to the Medication Information in the Guidelines for recommended starting dosages and dosage ranges.

9 For a general discussion of the clinical implications of polypharmacy, see reference 24. These include problematic pharmacokinetic/drug interactions, greater risk of side effects, increased costs. In those receiving combinations of atypicals and conventional antipsychotics, the risk of tardive dyskinesia is as great, or greater, than with conventional agents alone. In addition, when patients receive multiple medications, needed adjustments are difficult to make, and these regimens are associated with reduced medication adherence. A recent National Association of State Mental Health Program Director's report on polypharmacy discussed the problems associated with multiple antipsychotic use in state psychiatric hospitals and the steps that can be taken to reduce this (reference 25).

10 There is no empirical evidence for the use of combinations of antipsychotics. The concomitant use of two antipsychotics can only be recommended after patients have previously had an inadequate response to two or more adequate trials of monotherapy (preferably two trials of atypical and/or conventional agents followed by a trial of clozapine). Use of two antipsychotics concomitantly has some support from expert opinion, but this has not been recommended in any of the published practice guidelines until after trials of antipsychotic monotherapy and clozapine have been conducted.

11 Despite the better side effect profiles of the atypicals, serious adverse reactions can occur with these agents. Thus, although the incidence of EPS is lower with atypical antipsychotics, the benefits are not always seen when individuals are prescribed the atypical agents long-term ands/or in higher doses, and this is especially the case with

risperidone (reference 26). Naturalistic studies of their actual use demonstrate this best. One small community survey of individuals in long-term treatment with various antipsychotic agents, both atypical and conventional, has found high prevalence rates for parkinsonism, akathisia, and tardive dyskinesia, or T.D. A comparison of such prevalence rates with those of past decades suggests that these problems persist, despite the advent of newer agents with a lower propensity to produce extrapyramidal symptoms and T.D. (refer to references 27 and 28). Continuous monitoring of extrapyramidal side effects and T.D. is recommended for individuals who are being treated with atypicals (reference 29, 76).

12 Objective ratings of symptoms to help guide drug therapy are a standard component of several of the published practice guidelines, such as the Texas Medication Algorithm Project, or TMAP. For a discussion of the use of these rating tools and other evaluation instruments, see references 31-34.

13 Only one study of aripiprazole has been published (reference 30). More clinical experience with aripiprazole and additional trials are needed before its benefits and risks are established, so use caution prescribing this agent.

14 First-break patients are generally more responsive to treatment and require lower doses of antipsychotics than those with multiple psychotic episodes (references 13- 15).

15 Data from clinical trials of the antipsychotics demonstrate that most individuals will require 4 weeks or more of therapy, although a full response may require as long as 8 weeks. Since many individuals do not respond to clozapine within this timeframe, longer clozapine trials should be conducted. The recommendation is to slowly titrate the antipsychotic dose upwards; the use of a massive loading dose provides little therapeutic benefit and carries a higher risk of adverse reactions (references 10, 11, 14, 15).

16 Cross-tapering avoids the effects of a too abrupt withdrawal of the medication and reduces the effects of drug interactions. Rapid withdrawal of antipsychotics can produce a return of psychotic symptoms

and can also produce rebound effects; when clozapine is withdrawn too rapidly, rebound psychosis occurs and the symptoms are usually worse than those present before treatment. Pharmacodynamic and pharmacokinetic drug interactions can also occur when drugs are being switched. For a discussion of the issues involved in cross-tapering of antipsychotics, see references 10, 11 and 14.

17 About 30% of those individuals whose symptoms are unresponsive to other antipsychotics will respond to clozapine (reference 14).

18 All of the published practice guidelines make the recommendation for a clozapine trial after two or more trials of other antipsychotic agents are unsuccessful. Some of the guidelines suggest use of an atypical and a conventional agent before clozapine. The algorithm for the Texas Medication Algorithm Project, or TMAP, recommends that trials with several of the available atypical agents first precede a trial of clozapine. The DMHS Guidelines do not make a specific recommendation regarding use of particular agents in the antipsychotic trials that must precede clozapine use, as no evidence exists for such a recommendation. For further discussion of the issue of treating patients who do not respond to clozapine, see references 35-40.

19 While there are no controlled trials with ECT, there is empirical evidence that some individuals who do not respond to treatment with clozapine or other antipsychotics will respond to ECT (references 4, 39, 40). ECT may be associated with risks, but these are no greater than that with pharmacological therapy. However, since this empirical evidence is weak for its effectiveness in schizophrenia, use of ECT is only recommended as a last resort.

20 Few clinical trials have been conducted for the management of agitation or aggression. However, several open label studies, widespread clinical experience, and the recommendations of many experts support the use of intramuscular lorazepam because the drug is safe and effective. More recently, trial data has been published for use of intramuscular ziprasidone. While the agent also shows promise, this agent may be most useful in patients on oral ziprasidone who require a parenteral medication. More clinical experience with ziprasidone

is needed before it can be recommended with confidence (references 41-44).

21 The guidelines for the treatment of insomnia recommend non-pharmacological interventions and changes in patients' medication regimen (bedtime dosing) be attempted before adding a sedative-hypnotic agent (see reference 21). Melatonin has shown promise in aiding sleep in a small open label study of patients with schizophrenia (references 45 and 46).

22 The behavioral toxicity and other problems associated with benzodiazepines are well documented. Several of the published practice guidelines and standard psychopharmacologic texts comment about these effects. See reference 47 for an excellent review of the behavioral effects of benzodiazepines in individuals with mental retardation.

23 For a detailed description of the pharmacokinetics and pharmacodynamic differences seen in various racial and ethnic populations, see reference 48.

24 Maximizing the AP dose is necessary in order to treat positive symptoms. If the patient's positive symptoms do not improve, adding a mood stabilizer should be considered. However, the empirical evidence for the use of lithium and mood stabilizers in schizophrenia is weak. See the discussion in Note 28.

25 Atypicals have not been demonstrated to be more effective than conventional agents in treating negative symptoms. While the claim of such benefits continues to be made, the available empirical evidence suggests that the atypical agents are only more effective in reducing secondary negative symptoms. Primary negative symptoms correlate with the deficit syndrome of schizophrenia, but secondary negative symptoms may be due to a variety of causes, including EPS side effects, dysphoria secondary to psychosis or to antipsychotic medication, and/or a lack of environmental stimulation (references 9, 17, 18, and 21).

26 Catatonic symptoms in individuals with schizophrenia are more rarely seen today than in the past. These may occur less frequently today because in individuals being treated with antipsychotics, catatonic symptoms are usually attributed to the antipsychotic medication. Catatonic symptoms and parkinsonism are often seen during episodes of NMS, and the catatonic symptoms may persist for several weeks as a residual state following the acute hyperthermic stage of NMS (reference 65).

27 The recommendation of the DMHS Guidelines is to carefully assess the underlying cause(s) of persistent agitation or aggression and to treat these with non-pharmacological means before prescribing additional antipsychotic medication or other adjunctive treatment. See reference 53 for a description of these interventions.

28 The evidence base for the management of aggressive or impulsive behavior in schizophrenia includes few randomized, controlled clinical trials. Most of these recommendations are based on small, open studies, case series, and expert opinion. The greatest evidence for effectiveness in the treatment of hostility exists for clozapine, and all patients with persistent aggression that is resistant to treatment should be considered for a trial of clozapine (see references 54). Because few double-blind, controlled studies of lithium and the anticonvulsants as adjunctive agents with antipsychotics have been conducted in patients with schizophrenia, most of the empirical basis for their use is based on small open trials.. Lithium has been shown to be effective as an adjunctive agent with antipsychotics in several small trials, but the evidence is not conclusive. Carbamazepine is most effective in patients who have EEG abnormalities, but again the research base supporting such use in the treatment of schizophrenia is weak; also, since carbamazepine may lower serum levels of antipsychotics, careful dosing is necessary. Carbamzepine is contraindicated in patients receiving clozapine because of the greatly increased risk of agranulocytosis. Valproate is widely used as an adjunctive agent with antipsychotics; many clinicians see such use as an indicator that this drug is effective. However, the only evidence for its use in schizophrenia is based on small case series and open label studies. The few trials that have been done are inconclusive. Although the results of an unpublished 28-day double-blind, random-

ized trial of divalproex combined with olanzapine and with risperidone have been cited by the manufacturer as indicating that divalproex produces added benefits early in therapy, this short-term trial does not prove that the adjunctive use of this agent is superior to antipsychotic monotherapy. The other anticonvulsants have only small case series or case reports to recommend their use in patients with schizophrenia. In general, lithium and anticonvulsants are probably most effective when there is clear evidence of an underlying mood disorder and/or of EEG changes. For a description of studies that address the effectiveness of lithium and anticonvulsants in the treatment of schizophrenia, see references 14,15, 36, 38, 40, and 54.

29 As noted above, the specific anti-aggressive effects of clozapine in patients with schizophrenia is based on some evidence from clinical trials (references 6, 18, and 55).

30 Studies suggest that high dose propranolol can reduce aggression in psychiatric patients, especially in those with developmental disorders and brain trauma. Concomitant use of beta-blockers and antipsychotics can raise the blood levels of the latter. Also, beta-blockers should not be abruptly stopped, as this has been associated with the development of arrythmias and with sudden death (references 14, 15, 56).

31 The treatment of anxiety in schizophrenia is largely based on expert opinion, as little empirical evidence exists for these recommendations. These recommendations are consistent with those of other published practice guidelines and standard psychopharmacologic texts (references 4-15).

32 There are few studies of the treatment of obsessive-compulsive symptoms in patients with schizophrenia. However, first consider if these symptoms have been exacerbated by treatment with an AP, especially clozapine. Open label studies with adjunctive SSRIs suggest that these agents can reduce obsessive-compulsive symptoms, and there are also small clinical trials that demonstrate the effectiveness of concomitant of fluvoxamine and of clomipramine in patients with schizophrenia. However, clomipramine has many side effects

and can be lethal in overdoses. Consider drug interactions when adding an SSRI to an AP; fluvoxamine added to clozapine can raise the blood levels of the latter and cause a toxic reaction (references 57 and 58).

33 Cognitive deficits are occasionally seen in individuals with schizophrenia, and cognitive effects are also commonly associated with dopamine blockade and other actions of antipsychotic agents; cognitive effects most often occur during the use of antipsychotic agents in the elderly. Studies suggest that cognitive deficits are best managed by the use of atypical antipsychotics, except possibly for clozapine (references 63 and 64).

34 Before considering the need for medication, conduct an evaluation of the patient in order to make a differential diagnosis of depression; the patient may be reacting to a recent loss or be experiencing a temporary stress or a disappointment. Substance use, medications, and underlying physical illness can precipitate depression, and negative symptoms and EPS side effects can mimic depression. Stabilizing any psychotic symptoms is necessary before treating depression. Note that clozapine has received FDA approval for an indication for effectiveness in the prevention of suicide (reference 59-61).

35 There are small open label trials suggesting that both tricyclics and SSRIs can be effective as adjunctive agents. However, some patients have increased agitation as a result of antidepressant use, and these agents can exacerbate psychotic symptoms. Also consider that tricyclics have a number of side effects and that these agents and the SSRIs can cause drug interactions (see references 4, 14).

36 Substance use is very common among individuals with schizophrenia and is associated with a number of medical ands social problems. Current evidenced-based practices for those with dual disorders recommends that treatment for mental illness and substance abuse be integrated and provided by the same clinicians. See reference 52 for a discussion of substance abuse issues and integrated treatment for dual disorders.

37 Polydipsia is difficult to treat and requires close monitoring to protect patient safety. The only available trials of clozapine in polydipsia are inconclusive because these are short term studies. Use of propranolol in the treatment of polydipsia is only supported by small, open label trials. There are a couple of studies indicating promise for the use of naloxone injections, but this recommendation needs further validation and the use of this agent is not practical at this time (references 66-70).

38 These recommendations are not based on empirical evidence. However, these recommendations for a workup in patients who appear refractory to treatment with antipsychotics follow those in other practice guidelines, such as TMAP (references 10 and 11) and the New York Downstate Alliance (reference 13).

39 See reference 4, 38, 39

40 Non-adherence to prescribed psychotropic medication is very common and needs to be continually assessed. Studies suggest that about half of outpatients who are receiving psychotropic medications become non-adherent within the first six months of therapy. Individuals may become either partially adherent and just miss taking doses, or they may stop taking their medications altogether. These recommendations require practitioners to formally assess adherence using a variety of indicators, and then to take specific actions to address this issue. In order to address these issues, practitioner must develop a collaborative relationship with consumers and involved family members. For details about adherence assessment and interventions, see references 49-51.

41 Numerous clinical trials have confirmed the benefits of maintenance therapy with antipsychotics after initial control of acute symptoms; however, only a few long-term studies have been conducted. These demonstrate that continued treatment with antipsychotics will reduce relapse rates after the first year of treatment (references 4 and 6).

42 In addition to there being few randomized controlled trials of antipsychotics in the maintenance treatment of schizophrenia, only one long-term comparative trial with antipsychotics has been con-

ducted; this was a recent trial that has demonstrated superiority of treatment with risperidone over haloperidol in reducing relapse (reference 71).

43 Few trials have been conducted to assess relapse in patients on depot antipsychotics, and most of these studies were conducted in the past and have methodological limitations (reference 51). One recent meta-analysis of these trials suggests that global treatment response with depot agents was only slightly greater than that for oral agents, and that the evidence that these drugs are more effective in prevention of relapse was not statistically significant (reference 72). No one depot agent was demonstrated to be more effective than another. Furthermore, patients treated with the depot agents had a greater risk of experiencing movement disorders than those on oral antipsychotics (see reference). Although strong empirical evidence to demonstrate that depot antipsychotics can reduce relapse rates is lacking, these medications are clearly useful in a subpopulation of consumers with schizophrenia who do not adhere to their medication regimens.

44 The clinical trials of antipsychotic maintenance therapy have demonstrated that lower dosages (<300 mg chlorpromazine equivalents) are associated with greater probability of relapse. However, high dosages (>1000 mg chlorpromazine equivalents) offer no advantages in preventing relapse (references 6, 14, 15).

45 For a discussion of the empirical evidence supporting recommendations for the duration of maintenance treatment, see references 6, 73-75.

46 Recommendations for the management of breakthrough symptoms are based on expert consensus and are not supported by empirical evidence.

47 In addition to findings from short-term trials, information about side effects is based on the cumulative experience of practitioners. Recommendations for the management of side effects is from expert consensus, for the most. The recommendations in the DMHS Guidelines are consistent with those in other practice guidelines and from

standard psychopharmacology texts (references 4 -15). The format for the table is largely modeled on the tables that appear in references 13 and 14.

48 As discussed (see discussion in note 11), extrapyramidal symptoms, or EPS, are still seen in patients treated with atypical agents.

49 As demonstrated in a number of clinical trials, patients who are treated with clozapine have a very low risk of developing T.D. When patients who develop T.D. on other antipsychotics are switched to clozapine, these symptoms are often ameliorated or eliminated (references 77-79). There are some trials of patients with T.D. who were switched from conventional agents to atypical agents, and many of these individuals improve; however, the response using atypicals other than clozapine is variable (reference 4, 19).

50 Unlike the evidence for the effectiveness of clozapine in treating T.D., the empirical evidence for the use of vitamin B6 and melatonin is weak. However, these agents do show some promise in small trials, so their use can be recommended if other treatment of T.D. is not successful. Despite some recommendations by experts that vitamin E therapy of T.D. is effective, a recent meta-analysis of studies with vitamin E does not substantiate this claim (see references 80 and 81).

51 NMS can occur with the use of any antipsychotic, including the newer atypical agents, as shown by case reports. Recommendations regarding the rechallenge with antipsychotics after an episode of NMS are based on case reports and clinical experts. However, the literature may be biased due to the lack of reporting. Some experts recommend that the atypical agents be used during rechallenges, unless the patient has experienced a past episode of NMS with a particular atypical agent. They recommend use of a low potency conventional agent if atypical use is contraindicated. For further recommendations on evaluating and managing NMS, see references 82 and 83.

52 Anticholinergic effects are the cause of dry mouth, urinary retention, tachycardia, blurred vision, postural hypotension, and confusion, especially in the elderly. These effects are most prominent with the low potency conventional agents. Note that postural hypotension

can also occur as a result of alpha-adrenergic blockade, which can be seen with use of risperidone and high potency antipsychotics. For a discussion of anticholinergic side effects in elderly patients, see reference 84.

53 Hypersalivation, resulting in drooling, occurs usually as a dose-related effect of alpha-adrenergic blockade. Swallowing problems need to be ruled out (references 14, 15 and 86).

54 Sexual side effects and dysfunction are very common in those who are receiving psychotropics. Factors that care responsible for sexual side effects are complex. Many psychotropic medications cause autonomic side effects or have other physiological effects that cause sexual dysfunction. The sexual side effects of antipsychotic agents are related to these agents' anti-cholinergic and anti-dopaminergic effects, which also produce elevations of prolactin (references 15 and 85). Also, many individuals with schizophrenia have negative symptoms and may also be experiencing depression, which can result in a loss of sexual interest. Individuals with schizophrenia may also have co-occurring substance abuse problems that affect the ability to function sexually. The concurrent use of other psychotropics, including antidepressants, can also cause sexual problems.

55 The precise mechanism for altered glucose metabolism as a result of therapy with APs is not known. Glucose intolerance is seen much more frequently today than in the past because of the more widespread use of atypical agents. Risk of glucose intolerance is greatest in patients who are on Olanzapine and clozapine, but patients on risperidone are also at risk. The risk is increased when there is concomitant use of valproic acid, SSRIs, or buspirone. Note that the weight gain produced by the AP agents is not necessary in order for individuals to have glucose intolerance (references 87-89). Refer to the Monitoring and Laboratory Testing Protocols for antipsychotics for further recommendations on monitoring patients for glucose intolerance.

56 Weight gain is one of the more common side effects that occur with antipsychotics, especially in individuals who are receiving olanzapine and clozapine. Weight gain is seen early in treatment

with these antipsychotics (especially in the first year), but can occur anytime. Weight gain of 10 to 20 pounds is not uncommon, and some patients will gain as much as 40 or 50 pounds in the first year of treatment, especially when they also are on other medications that can also cause weight gain. Thus, most antidepressants, as well as mood stabilizers like valproate, can cause weight gain. Also, agents like paroxetine that can increase blood levels of antipsychotics can also cause weight gain as a result. Note that the weight gain produced by the antipsychotic agents is not necessary in order for individuals to have glucose intolerance. Furthermore, weight gain does not necessarily correlate with severity of hypertriglyceremia. Refer to the Monitoring and Laboratory Testing protocols for antipsychotics for further recommendations (references 90-92).

57 Sudden cardiac death occurs in greater frequency in patients receiving antipsychotics than it does in the general public, and those on agents like thioridazine are especially at risk. Ziprasidone is seen to cause a prolonged QTc interval, but the clinical significance of this is not fully known. Epidemiological studies of mortality in schizophrenia suggest that the risk of death increases greatly with the use of more than one antipsychotic, and this is a much greater risk factor than dose or duration of treatment (reference 93). It is believed that most cases of sudden death that occur in patients being treated with antipsychotics are the result of ventricular arrythmias, and that torsade de pointes is a likely precursor to ventricular arrythmias in treated patients (see references 94-97). Bundle branch block can also occur. Whenever symptoms occur suggesting cardiac effects, or whenever EKGs show a prolonged QTc interval or other EKG signs (e.g. bundle branch block and elevation of ST segment), these patients will need to have the antipsychotic stopped and should be evaluated by a cardiologist. Myocarditis and cardiomyopathy have also rarely been reported as adverse reactions during antipsychotic therapy; one review of a large database of such reactions demonstrated that clozapine use presented the greatest risk, although fluphenazine, chlorpromazine, haloperidol, and risperidone were also highly associated with these events, as was lithium (see reference 98). Antipsychotic agents, especially clozapine, are also rarely associated with venous thrombosis. The underlying biological process for this

is unknown. Any patient with dyspnea or chest pain should be evaluated for pulmonary embolism (see reference 99).

58 Liver dysfunction can occur in treatment with antipsychotics, especially during the first few weeks or months of therapy, because these agents are metabolized in the liver. Most expert opinion suggests that monitoring be done routinely to detect such hepatic dysfunction. Small elevations in transaminases, especially of ST (aspartate aminotransferase and/or alanine aminotransferase), are not uncommon, and these usually return to normal after several weeks. Thus, such elevations should be monitored but usually do not require a change in treatment. However, elevations of transaminases 2-3 times baseline levels, or any elevations in bilirubin or in alkaline phosphatase (ALP), should be carefully evaluated and underlying medical disorders ruled out.

59 Withdrawal effects are especially pronounced with clozapine, but can occur with any antipsychotic. In clozapine, too rapid withdrawal can result in agitation and rebound psychosis (reference 14).

60 According to one small study, injections with depot haloperidol are less painful than those with fluphenazine decanoate (reference 100).

61 These recommendations for managing pregnancy in women with schizophrenia are based on those in the literature (references 14, 15, 95, 101, and 102).

62 The recommendation to use blood level monitoring of antipsychotic therapy is based on expert opinion, and it is a recommendation that is made in most of the published schizophrenia practice guidelines and in standard psychopharmacology texts (references 4 -15).

63 Monitoring and laboratory testing guidelines are based on recommendations from other practice guidelines and from standardized psychopharmacology texts (references 4-15). Most of these are based on expert opinion, although some laboratory testing requirements are FDA-recommended package labeling.

64 For comparative side effects of antipsychotics, see reference 14.

65 Medication Information Tables References for these monitoring recommendations include published practice guidelines, standard psychiatric texts, and pharmacotherapeutic reference books, such as the Physician Desk Reference (references 4 –15, 104, and 105).

66 The use of antiparkinson agents for EPS are based on recommendations from published practice guidelines and standard psychiatric texts (references 4–15, and 76).

67 The AIMS+ is a rating tool that assesses both EPS and TD. See Fundamentals of Psychiatric Treatment Planning (reference 107).

REFERENCES

1. Mellman TA, Miller AL, Weissman EM, et al. Evidenced-based pharmacological treatment for people with severe mental illness: a focus on algorithms. Psychiatric Services 2001; 52(5): 619-25.

2. Milner KK, Valenstein M. A comparison of guidelines for the treatment of schizophrenia. Psychiatric Services 2002; 53 (7): 888-90.

3. Shekelle PG, Woolf SH, Eccles M, et al. Clinical guidelines: developing guidelines. BMJ 1999; 318: 593-6.

4. American Psychiatric Association. Practice guideline for the treatment of patients with schizophrenia. Second addition Am J Psychiatry 2004;161(2, suppl.).

5. Working Group for the Canadian Psychiatric Association and Canadian Alliance for Research in Schizophrenia. Canadian clinical practice guidelines for the treatment of schizophrenia. Can J Psychiatry 1998;43 (suppl 2): 25-40S.

6. Lehman AF, Steinwachs DM. Translating research into practice: the Schizophrenia Patient Outcomes Research Team (PORT) treatment recommendations. Schizophr Bull 1998;24: 1-10.

7. McVoy JP, Schleifer PL, Frances A. The Expert Consensus Guideline Series: treatment of schizophrenia. J Clin Psychiatry 1999;60 (suppl 11):1-80.

8. Pearsall R, Glick ID, Pickar D, et al. A new algorithm for treating schizophrenia. Pharmacology Bull 1998;34 (3): 49-53.

9. Marder SR, Essock S, Miller AL, et al. The Mount Sinai conference on the pharmacotherapy of schizophrenia. Schizophrenia Bull 2002; 28 (1): 5-15.

10. Miller AL, Chiles JA, Chiles JK, et al. The Texas Medication Algorithm Project (TMAP) schizophrenia algorithms. J Clin Psychiatry 1999;60: 649-57.

11. Miller AL, Chiles JA, Chiles J, et al. Texas medication procedures manual: schizophrenia module. Revised December 1999.

12. Toprac MG, Rush AJ, Conner TM, et al. The Texas Medication Algorithm Project patient and family education Program: a consumer-guided initiative. J Clin Psychiatry 2000: 61:477-86.

13. New York State Office of Mental Health Downstate Alliance and Guidelines Subcommittee. Recommendations for the pharmacological management of schizophrenia. New York State Office of Mental Health Downstate Alliance and Bureau of Evidenced-based Medicine and Clinical Guidelines 2001. Albany, NY.

14. Janicak PG, David JM, Preston SH, et al. Principles and practice of psychopharmacotherapy. Lippincott, Williams & Williams, Philadelphia, 2001.

15. Pies RW. Handbook of Essential Psychopharmacology. American Psychiatric Press, Inc. 1998. Washington DC.

16. Stanniland C, Taylor D. Tolerability of atypical antipsychotics. Drug Safety 2000; 22 (3): 195-214.

17. Geddes J, Freemantle N, Harrison P, et al. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. BMJ 2000; 321: 1371-6.

18. Buchanan RW, Brier A, Kirkpatrick B, et al. Positive and negative symptom response to clozapine in deficit and

non-deficit patients. Amer J Psychiatry 1998;155: 751-60.

19. Chakos M, Lieberman J, Hoffman E, et al. Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomized trials. Am J Psychiatry 2001;158 :518-526.

20. Azorin JM, Spiegel R, Remington G, et al. A double-blind comparative study of clozapine and risperidone in the management of severe chronic schizophrenia. Am J Psychiatry 2001;158 (8):1305-1313.

21. Carpenter WT. The treatment of negative symptoms: pharmacological and methodological issues. Brit J Psychiatry 168 (Suppl 29): 17-22.

22. Volavka J, Czobor P, Scheitman P, Lindenmayer JP. Clozapine, olanzapine, risperidone, and haloperidol in the treatment of patients with chronic schizophrenia. Amer J Psychiatry 2002:159(2): 255-262.

23. Taylor DM, Duncan-McConnell D. Refractory schizophrenia and atypical antipsychotics. J Psychopharm 2000;14(4): 409-18.

24. Miller AJ, Craig CS. Combination antipsychotics: pros, cons, and questions. Schizophrenia Bull 2002;28(1): 105-9.

25. Medical Directors Council. National Association of State Mental Health Directors. Technical Report on Psychiatric Polypharmacy, 2001.

26. Schillvoort I, de Boer A, Hennings R. Risk of extrapyramidal syndromes with haloperidol, risperidone, or olanzapine. Ann Pharmacotherapy 2001; 35: 1517-22.

27. Halliday J, Farrington S, Macdonald S, et al. Nithsdale Schizophrenia Surveys 23: movement disorders. Brit J Psychiatry 2002; 181: 422-7.

28. Bobes J, Reja J, Garcia M, et al. Frequency of adverse reactions in schizophrenic outpatients treated with risperidone, olanzapine, quetiapine, or haloperidol; results of the Eire study. Clin Drug Invest 2002; 22 (9): 609-22.

29. Weiden PJ, Miller AL. Which side effects really matter? Screening for common and distressing side effects of antipsychotic medications. J Psychiatric Practice 2001;7: 41-47.

30. Kane JM, Carson WH, Saha AR, et al. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. J Clin Psychiatry2002; 69(9): 763-771.

31. Roy-Byrne P, Dagadakis C, Ries R, et al. A psychiatrist-rated battery of measures for assessing the clinical status of psychiatric inpatients. Psychiatric Services 1995;46 (3): 347-52.

32. Serper MR, Allen MH. Rapid screening for cognitive impairment in the psychiatric emergency service: I. Cognitive screening batteries. Psychiatric Services 2002; 53: 1527-1529.

33. Bigelow LB, Berthot BD. The psychiatric symptom assessment scale. Psychopharm Bull 1989;25: 168-79.

34. Endicott J, Spitzer R, Fleiss J, et al. The global assessment scale : a procedure for measuring overall severity of psychiatric disturbance. Archives of Gen Psychiatry 1976;33: 766-71

35. Wirshing DA, Marshall BD, Green MF, et al. Risperidone in treatment-refractory schizophrenia. Amer J Psychiatry 1999;156: 1374-79.

36. Williams W, Newton G, Roberts K, et al. Clozapine-resistant schizophrenia: a positive approach. Am J Psychiatry 2002;181:184-7.

37. Buckley P, Miller A, Olsen J, et al. When symptoms persist: clozapine augmentation strategies. Schizophrenia Bull 2000; 27(4): 615-28.

38. Johns CA, Thompson JW. Adjunctive treatments in schizophrenia: pharmacotherapies and electroconvulsive therapy. Schizophrenia Bull 1995; 21 (4): 607-19.

39. Parker V, Remington G. ECT in clozapine treatment-resistant psychosis. Can J Psychiatry 2001; 46 (8): 762-3.

40. Dewan MJ, Pies RW, editors. The difficult to treat psychotic patient. American Psychiatric Press, 2002. Washington, DC

41. Battaglia J, Moss S, Rush, et al. Haloperidol, lorazepam or both for psychotic agitation? A multi-center, double-blind, emergency department study. Amer J Emerg Med 1997; 15 (4): 335-40.

42. Hamish-McAllister R, Ferrier IN. Rapid tranquilization: time for reappraisal of options for parenteral therapy. Brit J Psychiatry 2001;179: 285-9.

43. Brook S, Lucey JV, Gunn KP, et al. Intramuscular injections of ziprasidone compared with intramuscular haloperidol in the treatment of acute psychosis. J Clin Psychiatry 2000; 61: 933-41.

44. Currier GW, Simpson GM. Risperidone liquid concentrate and oral lorazepam versus intramuscular haloperidol for treatment of psychotic agitation. J Clin Psychiatry 2001; 62 (3): 153-7.

45. Kupfer DJ, Reynolds CF. Management of insomnia. New Eng J Med 1997; 336 (5): 341-6.

46. Shamir E, Laudon M, Barak Y, et al. Melatonin improves sleep quality of patients with chronic schizophrenia. J Clin Psychiatry 2000; 61 (5): 373-7.

47. Kalachik JE, Hanzel TE, Severnich R, et al. Benzodiazepine behavioral side effects: review and implications for patients with mental retardation. Amer J Mental Health 2002;107 (5): 376-410.

48. Burroughs VJ, Maxey RW, Levy RA. Racial and ethnic differences in response to medicines: towards individualized pharmaceutical treatment. J Nat Med Assoc 2002; 98 (10; suppl): 1-26.

49. Cramer J, Rosenbeck R. Compliance with medication for mental and physical disorders. Psychiatric Services 1998; 49 (2): 196-201.

50. Zygmunt A, Olfson M, Boyer C, et al. Interventions to improve medication adherence in schizophrenia. Am J Psychiatry 2002;159: 1553-64.

51. Valenstein M, Copeland LA, Owen R, et al. Adherence assessment and the use of depot antipsychotics in patients with schizophrenia. J Clin Psychiatry 2001; 62: 545-51.

52. Drake RE, Mercer-McFadden C, Muesaer K, et al. Review of integrated mental health and substance abuse treatment for patients with dual disorders. Schizophrenia Bull 1998; 24 (4): 589-607.

53. Corrigan PW, Yudofsky SC, Silver JM. Pharmacological and behavioral treatments for aggressive psychiatric inpatients. Hospital and Community Psychiatry 1993; 44 (2): 125-133.

54. Moeller FG, Barratt ES, Dougherty DM, et al. Psychiatric aspects of impulsivity. Am J Psychiatry 2001;158:1783-93.

55. Citrone L, Volavka J, Czobor P, et al. Effects of clozapine, olanzapine, risperidone, and haloperidol on hostilly annoyed patients with schizophrenia. Psychiatric Services 2001;51 (11): 1510-14.

56. Sergi PJ, Ratey JJ, Polakoff S. Beta-adrenergic blockade for the control of aggressive behavior in patients with chronic schizophrenia. Am J Psychiatry 1986; 143: 145-6.

57. Piccinelli M, Stefano P, Bellantuono C, et al. Efficacy of drug treatment in obsessive-compulsive disorder; a meta--analytic review. Brit J Pychiatry 1995;166: 424-443.

58. Berman I, Kalinowski A, Berman SM, et al. Obsessive and compulsive symptoms in chronic schizophrenia. Compr Psychiatry 1995: 36:6-10.

59. Hausmann A, Fleischhacker WW. Differential diagnosis of depressed mood in patients with schizophrenia: a diagnostic algorithm based on a review. Acta Psychiatr Scan 2002;106: 83-96.

60. Siris SG. Depression in schizophrenia: perspective on the era of "atypical" antipsychotic agents. Am J Psychiatry 2000; 167: 1379-89.

61. Escamilla MA. Diagnosis and treatment of mood disorders that co-occur with schizophrenia. Psychiatric Services 2001; 52 (7): 911-19.

62. Meltzer HY. Suicidality in schizophrenia: a review of the evidence and treatment options. Curr Psych Rep: 4: 279-83.

63. Harvey PD, Keefe RS. Studies of cognitive changes in patients with schizophrenia following novel antipsychotic treatment. Am J Psychiatry 2001;158 (2): 176-84.

64. Bilder RM, Goldman RS, Volavka J, et al. Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. Am J Psychiatry 2002;159 (6): 1018-28.

65. Caroff SN, Mann SC, Keck PE, et al. Residual catatonic state following neuroleptic malignant syndrome. J Clinical Psychopharmacology 2000; 20 (2): 257-9.

66. De Leon J, Dadvand M,Canuso C et al. Polydipsia and water intoxication in a long-term psychiatric hospital. Biol Psychiatry 1999; 40: 28-34.

67. Vieweg WR. Treatment strategies in the polydipsia syndrome. J Clin Psychiatry 1994; 55:154-9.

68. Spears NM, Ledbetter RA, Shutty Jr. MS. Clozapine treatment in polydipsia and intermittent hyponatremia. J Clin Psychiatry 1996; 57: 123-8.

69. Nishikawa T, Tsuda A, Tanaka M, et al. Involvement of the endogenous opioid system in the drinking behavior of displaying self-induced water intoxication; a double-blind controlled study with naloxone. Clin Neuropharmacol 1996; 19: 252-8.

70. Hayashi T, Nishikawa T, Koga I, et al. Involvement of the alpha-adrenergic system in polydipsia in schizophrenic patients: a pilot study. Psychopharmacology 1997; 130: 382-6.

71. Csansky JG, Mahmoud R, Brenner R. A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. N Engl J Med 2002; 346 (1): 16-22.

72. Adams CE, Fenton MK, Quraishi S, et al. Systematic meta-review of depot antipsychotic drugs for people with schizophrenia. Brit J Psychiatry 2001:179: 290-9.

73. Kissling W, Kane JM, Barnes TRE, et al. Guidelines for neuroleptic relapse prevention in schizophrenia: towards a consensus view, in guidelines for neuroleptic relapse prevention in schizophrenia, edited

by Kissling W., Berlin, Springer-Verlog, 1991, pp155-163.

74. Robinson D, Woerner M, Alir J, et al. Prediction of relapse following a first episode of schizophrenia or schizoaffective disorder. Arch Gen Psychiatry 1999; 56: 241-6.

75. Remington G, Kapur S, Zipursky RB, et al. Pharmacotherapy of first-episode schizophrenia. Brit J Psychiatry 1998; (33 Suppl): 66-70.

76. Stanill JK, Simpsom GM. Treatment of extrapyramidal effects, in Essentials of Clinical Psychopharmacology. Edited by Schatzberg AF, Nemeroff CB. Washington DC, American Psychiatric Press, Inc, 2001.

77. Egan MF, Apud J, Wyatt RJ. Treatment of tardive dyskinesia. Schizophrenia Bull 1997; 23(4): 583-609.

78. Casey DE. Effects of clozapine therapy in schizophrenic individuals at risk for tardive dyskinesia. J Clin Psychiatry 1998; 59 (suppl 3): 31-7.

79. Kane JM, Woerner MG, Pollock S, et al. Does clozapine cause tardive dyskinesia? J Clin Psychiatry 1993;54(9): 327-30. 2002; 181: 422-7.

80. Lemer V, Miodewnik C, Kapstan A, et al. Vitamin B6 in the treatment of TD: a double-blind, placebo-controlled, crossover study. Am J Psychiatry 2001;158 (9): 1511-14.

81. Shamir E, Barak Y, Shalman I, et al. Melatonin treatment for TD: a double-blind, placebo-controlled, crossover study. Arch Gen Psychiatry 2001; 58 (11): 1049-1052.

82. Caroff SN, Mann SC, Campbell EC. Atypical antipsychotics and neuroleptic malignant syndrome. Psychiatric Annals 2000; 30(5): 314-321.

83. Hasan S, Buckley P. Novel antipsychotics and the neuroleptic malignant syndrome: a review and critique. Am J Psychiatry 1998;155 (8): 1113-6.

84. Mintzer J, Burns A. Anticholergic side-effects of drugs in elderly people. J Royal Society Medicine 2000; 93: 457-63.

85. Smith SM, O'Keane V, Murray R. Sexual dysfunction in patients taking conventional antipsychotic medication. Briti J Psychiatry

86. Tsheng DZ. Sialorrhea-therapeutic drug options. Ann Pharmacotherapy 2002; 36: 1785-1789.

87. Ragucci KR, Wells BJ. Olanzapine-induced ketoacidosis. Ann Pharma-cotherapy 2001; 35: 1556-8.

88. Wirshing DA, Boyd JA, Meng LR. The effects of novel antipsychotics on glucose and lipid levels. J Clin Psychiatry 2002; 63(10): 856-65.

89. Hedenmalm K, Hagg S, Stahl. M. Glucose intolerance with atypical anti-psychotics. Drug Safety 2002;25 (15): 107-16.

90. Allison D, Mentore JL, Heo M, Chandler LP, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Amer J Psychiatry 1999;156 (11): 1686-96.

91. Henderson DC, Cagliero E, Gray C, Nasrallah RA, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. Amer J Psychiatry 2000;157(6): 975-81.

92. Vanina F, Podolskaya A, Sedky K. Body weight changes associated with psychopharmacology. Psychiatric Services 2002; 53: 842-7.

93. Waddington JL, Youseff Ha, Kinsella A. Mortality in schizophrenia; antipsychotic polypharmacy and abuse of adjunctive antidepressants over the course of a 10-year

prospective study. Br J Psychiatry 1998; 193: 325-9.

94. Zarate CA. Commentary: Sudden cardiac death and antipsychotic drugs. Do we know enough? Arch Gen Psychiatry 2001;(12); 58: 1168-71.

95. Glassman AH, Bigger OT. Antipsychotic drugs, prolonged QTc interval, torsade de pointes, and sudden death. Am J Psychiatry 2001; 158:1774-82.

96. Glassman AH. Clinical management of cardiovascular risks during treatment with psychotropic drugs. J Clin Psychiatry 2002;63(suppl 9):12-17.

97. Reilly RG, Ayis A, Ferrier IN, et al. Thioridazine and sudden unexplained death in psychiatric inpatients. Briti J Psychiatry 2002;180: 515-22.

98. Coulter DM, Bate B, Meyboom RH, et al. Antipsychotic drugs and heart muscle disorder in international pharmacovigilence: data mining study. BMJ 2001; 322: 1207-9.

99. Thomasson R, Vandenbrouke JP, Rosendaal FR. Antipsychotic medication and venous thrombosis. Brit J Psychiatry 2001; 179: 63-6.

100. Bloch Y, Mendlovic S, Strupinsky S, et al. Injections of depot antipsychotic medications in patients suffering from schizophrenia: do they hurt? J Clin Psychiatry 2001;62:855-9.

101. Miller LJ. Psychiatric medications during pregnancy: understanding and minimizing risks. In Janicak PG, Davis JM (guest eds.). Psychiatric Annals 1994; 24: 69-75.

102. Koren G, Cohn T, Chitayat D, et al. Use of atypical antipsychotics during pregnancy and the risk of neural tube defects. Am J Psychiatry 2002; 159 (9): 136-7.

103. Cozza KL, Armstrong SC. Concise Guide to the Cytochrome P450 System; drug interaction principles for medical practice. 2001. American Psychiatric Press, Washington, DC.

104. Physicians Desk Reference. Montvale, NJ. Thomson Medical Economics Data Company, 2005.

105. 2002 Drug Topics Red Book. Montvale, NJ, Thomson Medical Economics Company, 2005.

106. American Psychiatric Association. Practice guidelines for the treatment of patients with schizophrenia. Second edition 2004 pages 17, 19, 67-69.

107. Kennedy, JA, Fundamentals of Psychiatric Treatment Planning. American Psychiatric Press, Washington, DC 1992.